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α-Cyclodextrin-I_3^- Host−Guest Complex in Aqueous Solution: Theoretical and Experimental Studies

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UV−vis spectroscopic studies on aqueous solutions of iodine, potassium iodide, and α-cyclodextrin (αCD), $(C_6H_{10}O_5)_6$, suggest that a complex forms with the composition of $\alpha CD_2I_3^-$. Semiempirical quantum mechanical PM3 calculations suggest that two major host−guest isomer types exist for this complex. The most stable isomer has the I_3^- ion oriented almost parallel to the plane of one of the αCD molecules and sandwiched between two αCD molecules. The second sandwich isomer is less stable than the above isomer by about 5 kcal/mol (20.9 kJ/mol) and has the I_3^- ion oriented vertically (along the vertical axis) between two αCD molecules. The formation constant (K_f) of the complex is determined to be around 7.0×10^8 M^{-2} for both 15 and 25 °C.

Introduction

Cyclodextrin (CD) is a cyclic nonreducing D-glucosyl polymer with α −(1→4) links. It has a hydrophilic outer surface and a hydrophobic inner cavity.[1−4] The α, β and γ are three most common types of CDs composed of 6, 7 and 8 D-glucopyranose ($C_6H_{10}O_5$) units, respectively. These ring shaped structures allow CDs to contain guest molecules and thus, to form inclusion complexes. The recent attention to complex forming reaction of CD stems from its innumerable uses that include drug delivery systems, fabric softeners, antibacterial sheets, removal of cholesterol in food production processes, recognition of amino acids, new compound synthesis,[5−10] etc. In addition, CDs serve as excellent models for enzymes as they form host−guest complexes with various substrates resulting in catalytic effects in many reactions.[2−4] The common CDs have molecular weights of around 1000 and are considerably larger than the conventional organic compounds but significantly smaller than enzymes having molecular weights of 10 000 to over 50 000. Hence, the CD molecules bridge the gap between ordinary organic compounds and enzymes. This is why quite a few studies have been undertaken to understand the complex forming reaction and also to determine the nature and composition of these complexes.

Most CD molecules provide 1:1, 1:2 or 2:1 complexes with various guests.[3,4,11−16] Although a large number of organic molecules are used as guests in most studies, very few studies are reported on inorganic molecules or ions such as iodine or iodides. Besides the academic interest, we are also motivated by recent reports that suggest potential applications of iodine species in the treatment of breast lesions.[17,18] The CD molecule by forming a complex can serve as a carrier of these species that may gradually release iodine at the body temperature.

Among the few relevant studies on iodine/iodide complex, the X-ray diffraction studies on crystal structure[19−21] suggest that the αCD /iodide complexes involve two αCD molecules and a polyiodide ion enclosed within the αCD cavity. The iodide species are considered to be (I_3^-.I_2), (I_2. I^-.I_2) or I_5^- ions with inter-iodine distance of around 3 Å.

Although the complex composition in the solid state is well established ($\alpha CD_2I_5^-$), the solution phase results are less conclusive. In an earlier absorption study by Thoma and French[22] the composition of αCD complexes with iodine species (I_2, I^-, I_3^-, etc.) are obtained by determining ratios such as I_2/ (I_2 + αCD) and I^-/(I_2 + I^-) for different absorbance values of the complex. A ratio of 0.50 at the point of maximum absorbance in each case suggests 1:1 combination of I_2 with αCD (giving αCDI_2, from first ratio) and 1:1 combination of I_2 with I^- (from second ratio). Even though the first ratio provides unambiguously the complex composition with I_2, the second ratio provides two different complex compositions with I_3^-. Because the second ratio was determined in the presence of an excess αCD in the solution, one needs to consider two possible reactions. If αCD and I^- do not form a complex, then 1:1 combination will involve αCDI_2 and I^- giving αCDI_3^-. On the other hand, if there is a complex like αCDI^- in addition to αCDI_2, the 1:1 combination will yield $\alpha CD_2I_3^-$. Thoma and French[22] considered the composition of the complex to be αCDI_3^- as they ignored the formation of αCDI^- complex on the ground that the absorbance peak shift for the complex formation (from that of the I^- solution) was not noticed. As the authors point out, the failure to observe any spectral shift may be due to a close similarity between the spectra of I^- and αCDI^-. The experiments of Sano et al.,[23] however, suggest the predominant formation of αCDI^- in the solution of I^- and hence, by combining this result with that of Thoma and French one can arrive at the alternative composition of $\alpha CD_2I_3^-$. Diard et al.[24] merely assumes a 1:1 complex composition for αCD/I_3^- complex and calculates formation constants. However, their consideration of αCDI^- and αCDI_2 in the solution (eqs 1 and 3 in ref 24) combined with Thoma and French's finding of 1:1 combination of I_2 and I^- species in αCD solution would lead to a $\alpha CD_2I_3^-$ (2:1) composition for the complex. The solution phase isothermal titration calorimetry study by Kitamura et al.[25] suggests the formation of 1:1 type complex between αCD and iodine (in the presence of KI) and 1:2 complex with much larger CD complexes (degree of polymerization of 21−32). From above discussions, we can say that the composition of αCD/I_3^- complex has not yet been known unambiguously. The experimental difficulties have been pointed out by Rekharsky and Inoue,[4] and may be responsible for the above

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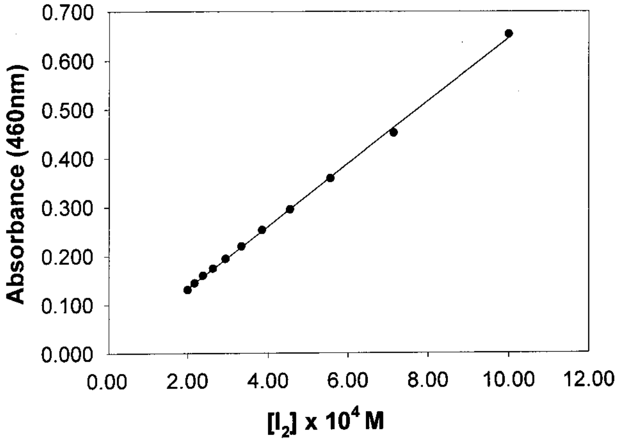

Figure 1. I_2 calibration graph obtained at 15 °C. The straight-line relationship suggests the validity of Beer−Lambert's law.

disagreements. It should be mentioned that the above study determines the complex composition by an indirect method and is subject to errors. One can also question the validity of some of the earlier findings on the stability ground of the αCDI_3^- complex (1:1 complex) relative to other possible compositions. Even though the X-ray diffraction study on solid crystal structure suggests the presence of two αCD molecules per I_5^- species, the composition in the solution phase can be different, especially when the I_5^- ions do not exist in the aqueous solution of iodine and KI.[26] From the above discussions, it is apparent that additional studies are required for determining the composition of the αCD complex with I_3^- species in the solution. The importance of aqueous phase inclusion compound formation provides the added incentive to undertake this project. The experimental composition studies are followed by theoretical investigation of the complex structure and its stability. To the best of our knowledge, this is the first theoretical study of this type to be reported on this important host−guest complex forming reaction.

Experiments, Results and Discussions

Composition of the Complex. The method applied here for determining the composition of the $\alpha CD/I_3^-$ complex is the same as that used for determining the composition of amylopectin−iodine and glycogen-iodine complexes.[27,28] The concentrated iodine solution used in composition experiments contains 6.62×10^{-4} moles/L (M) I_2 (diluted from a concentrated solution, Fisher SI86) and about 10 times more KI (diluted from concentrated, Fisher SP241, 0.3012 M). The above I_2 concentrations were determined by both titration with thiosulfate as well as absorbance measurements at 460 nm (15 °C), and using a calibration graph (Figure 1). The calibration graph was obtained at 15 °C for different iodine concentrations made from solid iodine, and shows a linear relationship (Beer−Lambert). The I_2 concentrations for Figure 1 were determined by titrations with thiosulfate and plotted against absorbance values at 460 nm.

In the presence of a large excess of KI all the molecular iodine used in composition experiments is changed to triiodide ions. This has been confirmed by absorbance measurements in the UV−vis region by using a Genesys 2 Spectrophotometer. The spectrum, presented in Figure 2, indeed shows only one peak at around 360 nm and as expected, no peak at 460 nm. It should be mentioned that the absorbance peak at around 360 nm is due to I_3^- ions and at 460 nm is due to I_2 molecules.[26]

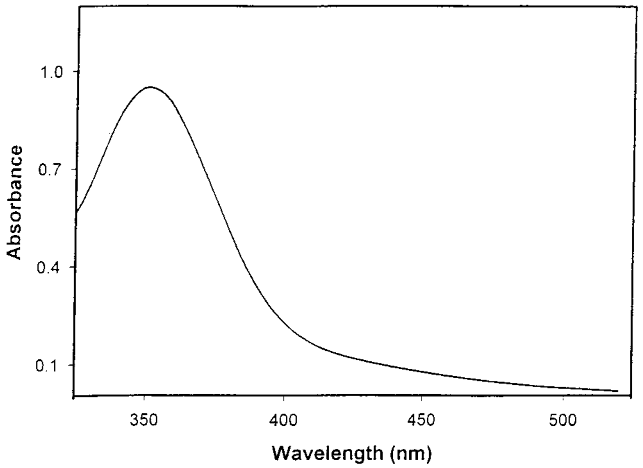

Figure 2. UV−vis spectrum of iodine solution in the presence of an excess KI. The only peak seen at around 360 nm is due to I_3^- ions in the solution. The absence of a peak at around 460 nm suggests nonexistence of I_2 molecules in the solution under our experimental conditions.

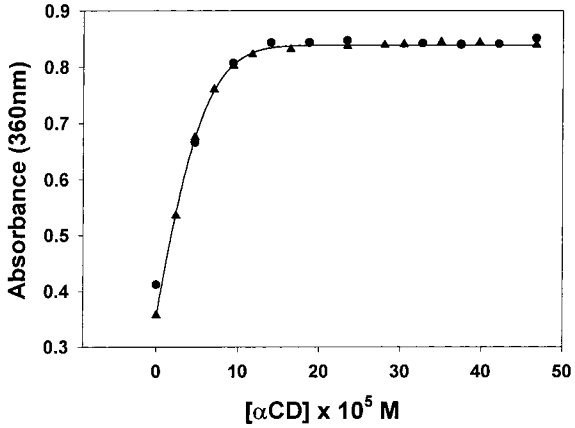

Figure 3. Composition curve for αCD complex with I_3^- ion. The absorbance at 360 nm is increased with the addition of αCD, and is then leveled off when all the I_3^- ions are bonded to the αCD molecules. The filled spheres and triangles represent data from 15 and 25 °C experiments respectively and the solid curve is fitted to one of the data sets primarily to guide our eyes. This result provides the complex composition of $\alpha CD_2I_3^-$.

In each 1 mL portion of the triiodide solution (6.62×10^{-4} M I_3^-) varied amounts (0−10 mL) of 5.14×10^{-4} M αCD solution (Sigma Chemical, C-4642, purity 100%) and rest water were added for a total volume of 11 mL at both 15 and 25 °C. The absorbance was then measured for each solution at 360 nm. In a separate experiment we established that the complex formation of triiodide with αCD only enhances the absorbance value at 360 nm by 2−3-fold and does not shift the peak position. This is expected when the host−guest complex does not change the electronic structure of the guest (triiodide ion) molecule in any significant way. Figure 3 represents the result of this experiment. As expected, the absorbance is first increased when the amount of complex in the solution is increased with the addition of αCD (for a fixed 6.02×10^{-5} M I_3^- in total 11 mL solution), and then, levels off when the complex forms to the maximum extent. At this point all the I_3^- ions in the solution become part of a complex with αCD molecules, and any additional αCD does not change the concentration or the absorbance of the complex. This saturation point corresponds to 6.02×10^{-5} M I_3^- ions and about 12.0×10^{-5} M α-CD and hence, provides the $\alpha CD:I_3^-$ ratio of 2:1. The filled circles and triangles represent data from 15 and 25 °C experiments and the solid fitted curve shows the trend of the data sets primarily to guide our eyes. Because of the closeness of the data, the curve fitting was done to one of the data sets only. Repeated composition experiments with 1 mL of other iodine solutions (8.28×10^{-4} and 10.0×10^{-4} M I_3^-) showed the same 2:1 composition ($\alpha CD_2I_3^-$) at both 15 and 25 °C (figures not presented), and establish the reliability of the method applied and stability of the complex at these temperatures.

Formation Constant (K_f) of $\alpha CD_2I_3^-$ Complex. On the basis of 2:1 composition of the complex we can write the following equilibrium expression

$$\mathbf{2\,\alpha CD + I_3^- = \alpha CD_2I_3^-} \; ..... \qquad (1)$$

$$K_f = [\alpha CD_2I_3^-]/([\alpha CD]^2[I_3^-]) \; ... \qquad (2)$$

where K_f is the formation constant of the complex in terms of equilibrium concentrations of reactants and products.

Figure 4 represents a calibration graph for the $\alpha CD_2I_3^-$ complex concentration. The data for this graph came from experiments at 15 °C that involved 3 times more αCD than I_3^- for various molar concentrations of I_3^-. Almost identical graph was obtained for experiments at 25 °C (not presented). At such a high αCD concentration, all of the I_3^- ions remain bonded to the complex giving the complex concentration same as that of the I_3^- ions (each complex molecule has one I_3^- ion). For determining the formation constant values moderate concentrations of αCD and I_3^- were used. The mixed solutions had I_3^- and αCD concentrations ranging from 1×10^{-4} to 2×10^{-4} M, and the absorbance value for each solution was taken at 360 nm. The measured absorbance value at 360 nm is due to both the $\alpha CD_2I_3^-$ complex (absorbs strongly) and the unbound triiodide ions (absorbs much less strongly) from which the unbound triiodide ion contribution was subtracted. We determined the triiodide ion contribution by first making its solution of the same concentration as that used in the complex formation, and then, measuring its absorbance at 360 nm. Each complex absorbance value was converted to its concentration by using the calibration graph of Figure 4. From the added amounts of αCD molecules and triiodide ions, the equilibrium concentrations were calculated as follows

$$[\alpha CD] = [\alpha CD]\text{added} - 2 \times [\alpha CD_2I_3^-]$$
$$\text{(two } \alpha CD \text{ bonded per } \alpha CD_2I_3^- \text{ complex)}$$

$$[I_3^-] = [I_3^-]\text{added} - [\alpha CD_2I_3^-]$$
$$\text{(one } I_3^- \text{ bonded per } \alpha CD_2I_3^- \text{ complex)}$$

The value of $[I_3^-]$added was obtained from the concentration of I_2 solution used in the experiment. The I_2 concentration was known from an absorbance measurement at 460 nm and by applying the calibration graph of Figure 1. The addition of excess KI ensured the conversion of all I_2 molecules to I_3^- ions. At this point, the 460 nm peak of I_2 disappeared and a large peak of 360 nm (for I_3^-) was observed. In one such experiment 3 mL of I_3^- (6.62×10^{-4} M I_2 + excess KI) was added to 4 mL αCD (5.14×10^{-4} M) and 11 mL H_2O. This gave $[I_3^-]$ added and [αCD] added values of 1.103×10^{-4} and 1.142×10^{-4} M, respectively. The absorbance for the $\alpha CD_2I_3^-$ complex at 360 nm was 0.549 (after subtracting absorbance due to I_3^- ions), which corresponds to $\alpha CD_2I_3^-$ concentration of 4.13×10^{-5} M (from Figure 4). These values provided a K_f value of around 6.0×10^8 M^{-2}. Similarly, the other K_f values were calculated giving an average of around 7.0×10^8 M^{-2}. The K_f values for both 15 and 25 °C are about the same with an average value of around 7.0×10^8 M^{-2}. A direct comparison of this value with that of Diard et al. or others ($1.7-3.6 \times 10^5$ M^{-1})[24] is not possible as those studies assume 1:1 complex composition between αCD and I_3^-.

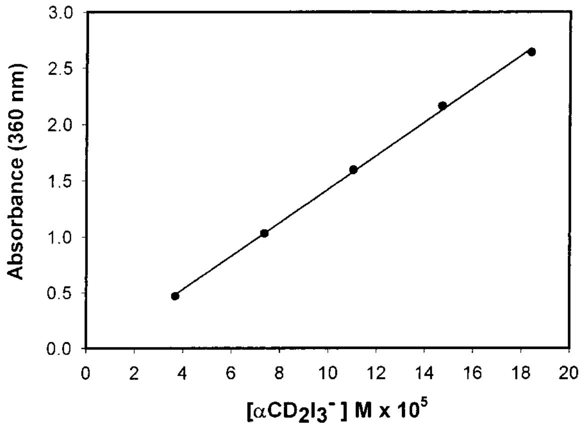

Figure 4. Calibration graph for $\alpha CD_2I_3^-$ complex obtained at 15 °C for an increasing concentration of I_3^- and a large excess of αCD. The experimental data points and the straight line fit to the data set are also shown. This graph is used for determining the formation constant for the $\alpha CD_2I_3^-$ complex. The 25 °C experiment gives almost an identical graph (not presented here).

Theoretical Studies: Structure of the Complex. The geometry optimizations and energy calculations (singlet states) are done by semiempirical quantum mechanical method,[29] PM3, in Hyperchem package[30] (version 5.0). Before applying this method, a number of tests are carried out to examine the reliability of the method.

Reliability Tests. The validity of the method has been examined by calculating structures and energies of a number of polyiodine and polyiodide species that have already been calculated by other methods. For example, the PM3 method predicts that the most stable I_5^- structure is V-shaped, and is in agreement with the other reported structures.[31] In addition, the V-shaped I_5^- structure is predicted to be more stable than the linear isomer by around 4.6 kcal/mol (19.2 kJ/mol). This value is in line (overestimated to some extent) with those obtained from the other methods of calculations.[31] Similarly, the I−I distance in the I_3^- ion is calculated to be (PM3) around 2.73 Å and is slightly shorter than the distance of 2.95−3.0 Å calculated by other methods.[31] A correction by +0.25 Å has been applied for a better representation of the I−I distances. Because of the large size of this problem involving iodine atoms, more accurate methods such as MP2/LANL2DZ//HF/LANL2DZ are found to be extremely time-consuming, and hence, inapplicable for the present system. From the above test results, however, we conclude that the PM3 structure and relative energy values are good enough to be trusted.

All the geometry optimizations are based on a number of assumed structures. Among the various structure types examined, the most stable ones are presented and discussed below:

Calculation of αCDI_3^- Structure. Two structure types of 1:1 complex composition (not shown) are examined. The assumed structure 1 has an I_3^- ion perpendicular to the plane of a αCD molecule (along the vertical molecular axis), and the structure 2 has the I_3^- ion parallel to the αCD plane. Although the optimized structure 1 is close to the assumed geometry, the optimized structure 2 shows a significant reorientation of the I_3^- ion from 90° to around 30° from the vertical axis. The optimized structure 2 is more stable by about 3 kcal/mol (12.6

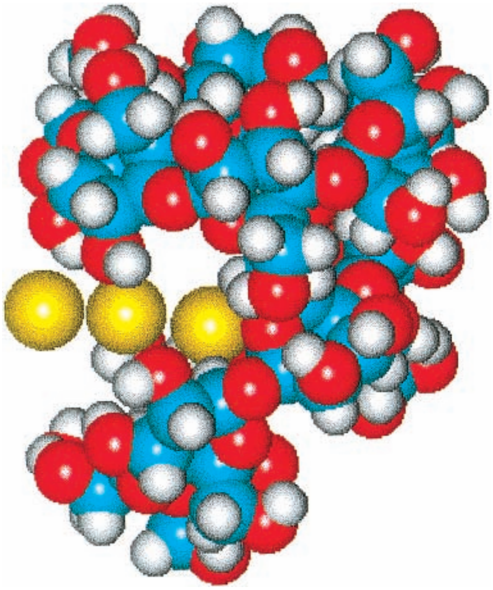

Figure 5. Most stable horizontal isomer for the $\alpha CD_2I_3^-$ complex. The I_3^- ion is oriented horizontally (larger spheres) along the plane of an αCD molecule.

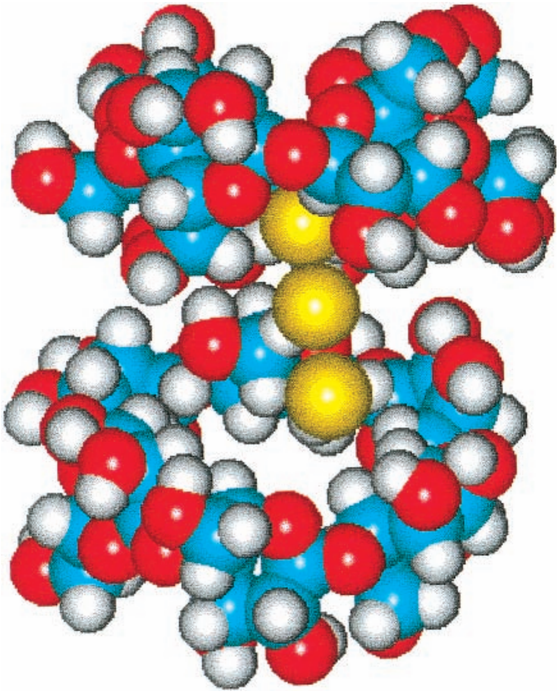

Figure 6. Second most stable vertical isomer for the $\alpha CD_2I_3^-$ complex. The I_3^- ion (large spheres) in this structure is oriented vertically along the vertical axis of the αCD molecules.

kJ/mol) than the optimized structure 1. The I—I—I angle in each complex is around 177° and suggests the presence of a linear triiodide ion within the complex. These complexes may form prior to the formation of a more stable 2:1 complex as described below.

Calculation of $\alpha CD_2I_3^-$ Structure. Two isomer structures are examined for the dimeric αCD complex (2:1) observed in the present experiment. The optimized structures look very similar to their starting geometries (Figures 5 and 6) and are more stable than the monomeric complexes (αCDI_3^-, discussed above) by about 15−18 kcal/mol (63−75 kJ/mol). The most stable dimeric structure type (horizontal isomer) is the one that has the I—I—I unit parallel to the plane of one αCD molecule (makes around 4° angle, Figure 5). It is about 5 kcal/mol (21 kJ/mol) more stable than the second isomer (vertical isomer, Figure 6) in which the triiodide unit is along the vertical axis. In each case, two αCD molecules form a sandwich type compound with the triiodide unit lying inside. In the horizontal structure the I—I—I angle is 174° and is slightly bent. As can be noticed in Figure 5, the αCD molecules in the complex are not quite parallel, rather they make an angle of around 26° with each other and are at a distance of around 11 Å (from centroid positions). The triiodide ion remains almost in the middle of two αCD molecules with the central iodine at a distance of around 5 and 6 Å from the top and the bottom αCD molecule, respectively.

In the vertical isomer (Figure 6) the I—I—I angle is around 177° suggesting almost a linear arrangement of a triiodide ion. The distance between two αCD molecules in the complex is around 10 Å, and the planes of the αCD molecules are almost parallel to each other making an angle of around 4°. This arrangement is significantly different from that of the horizontal isomer in which the angle between two αCD molecules is around 26°. The triiodide ion in vertical isomer is almost perpendicular to the plane of the αCD molecule and makes an angle of around 93° with the αCD plane. The I—I distance in each complex is around 3 Å and is almost the same as that obtained for an isolated triiodide ion.

Possible Solvent Effects on Complex Stability. Even though the present calculation does not consider solvent effects, one can postulate possible effects of solvents on the complex. In the 1:1 complex (αCDI_3^-), the I_3^- ion is weakly bonded to a αCD molecule and is exposed to the solvent and may become vulnerable to cleavage. The I_3^- ion in a 2:1 ($\alpha CD_2I_3^-$) complex, on the other hand, is sandwiched between two αCD molecules, and is more strongly bonded and less exposed to solvent molecules. Hence, the I_3^- ion in 2:1 complex is much less likely to be affected by solvent molecules than that in the 1:1 complex. Thus, both from the theoretical ground and experimental results we can conclude that the 2:1 type complex ($\alpha CD_2I_3^-$) is more likely to be present in an aqueous solution.

Concluding Comments. The αCD molecule forms a 2:1 complex with I_3^- ion. Theoretical studies suggest the formation of two sandwich type isomers each with an I_3^- ion inside. The most stable one has the I_3^- ion oriented almost parallel to the plane of one of the αCD molecules, and the second isomer has the I_3^- ion perpendicular to the αCD plane. Because of significant stability of the dimeric complex compared to the monomeric one, the primary structure type in the solution is expected to be dimeric with 2:1 composition ($\alpha CD_2I_3^-$). Indeed, the experimental results confirm this expectation. The complex is stable at both 15 and 25 °C with the formation constant value of around 7.0×10^8 M^{-2}.

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