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Is Introducing Crystal Structures of Ferrocene in Cyclodextrin into Learning Materials for STEM Education Possible?

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Abstract:

This study aimed to critically verify the validity of the widely used "Ferrocene in Cyclodextrin" (Fc in CyD) model in inquiry-based education within Science, Technology, Engineering, and Mathematics (STEM) fields, by examining available crystallographic data for inclusion compounds between Cyclodextrin (CyD) and Ferrocene (Fc). The methodology relied on a systematic review of scientific literature and a search of the Cambridge Crystallographic Data Centre (CCDC) database to verify reported molecular structures. The results revealed that the simplified educational model, which assumes specific inclusion ratios (e.g., 2:1 for α-CyD and 1:1 for β- and γ-CyD), is not conclusively supported by comprehensive crystallographic evidence; confirmed crystal structures exist only for α-CyD with Fc (2:1 ratio) and its oxidized form Fc^+, and for β-CyD with Fc but in a complex 4:5 ratio, whereas no X-ray crystallographic analysis confirming Fc inclusion within γ-CyD was found, despite spectroscopic and theoretical evidence suggesting their interaction. The study concludes that relying on the simplified model as an absolute truth in educational curricula may convey inaccurate information, and instead proposes using well-documented inclusion compounds of Fc/Fc^+ with α-CyD as alternative educational materials, given their support by robust structural and experimental data, thereby enhancing the accuracy of inquiry-based learning in organometallic chemistry and host-guest chemistry. The originality of this study lies in its being the first systematic critical review to verify the actual crystallographic support for the widely cited "Fc in CyD model" in education.

Keywords: *Crystal Structures; Ferrocene; Cyclodextrin; Learning Materials; STEM Education.*

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هل يمكن إدخال الهياكل البلورية للفيروسين في السيكلودكسترين ضمن المواد التعليمية لتعليم العلوم والتكنولوجيا والهندسة والرياضيات (STEM)؟

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ملخص:

هدفت هذه الدراسة إلى التحقق النقدي من صحة نموذج "الفيروسين في السيكلودكسترين" (Fc in CyD model) الشائع الاستخدام في التعليم القائم على الاستقصاء ضمن مجالات العلوم والتكنولوجيا والهندسة والرياضيات (STEM)، من خلال فحص البيانات البلورية المتاحة لمركبات الإدماج (inclusion compounds) بين السيكلودكسترين (Cyclodextrin – CyD) والفيروسين (Ferrocene – Fc). واعتمدت المنهجية على مراجعة منهجية للأدبيات العلمية والبحث في قاعدة بيانات مركز كامبريدج للبيانات البلورية (Cambridge Crystallographic Data Centre – CCDC) للتحقق من الهياكل الجزيئية المبلغ عنها. وكشفت النتائج أن النموذج التعليمي المبسط، الذي يفترض نسب إدماج محددة (مثل 2:1 لـ α–CyD و1:1 لـ β– وγ–CyD)، لا يدعمه بشكل قاطع دليل بلوري متكامل؛ إذ توجد هياكل بلورية مؤكدة فقط لمركب α–CyD مع Fc (بنسبة 2:1) ومع شكله المؤكسد Fc^+، ولمركب β–CyD مع Fc ولكن بنسبة معقدة (4:5)، بينما لم يتم العثور على أي تحليل بلوري بالأشعة السينية يؤكد إدماج Fc داخل γ–CyD، على الرغم من وجود أدلة طيفية ونظرية تشير إلى تفاعلهما. وتخلص الدراسة إلى أن الاعتماد على النموذج المبسط كحقيقة مطلقة في المناهج التعليمية قد ينقل معلومات غير دقيقة، وتقترح بدلاً من ذلك استخدام مركبات الإدماج الموثقة جيداً لـ Fc/Fc^+ مع α–CyD كمواد تعليمية بديلة، نظراً لدعمها ببيانات هيكلية وتجريبية رصينة، مما يعزز دقة التعلم القائم على الاستقصاء في الكيمياء العضوية الفلزية (organometallic chemistry) وكيمياء المضيف–الضيف (host–guest chemistry). تكمن أصالة هذه الدراسة في كونها أول مراجعة نقدية منهجية تتحقق من الدعم البلوري الفعلي لنموذج "الفيروسين في السيكلودكسترين" (Fc in CyD model) الشائع في التعليم.

الكلمات المفتاحية: *الهياكل البلورية؛ الفيروسين؛ السيكلودكسترين؛ المواد التعليمية؛ تعليم STEM.*

1. Introduction

Cyclodextrin (CyD) is a cyclic oligosaccharide composed of glucoside-bonded glucose units, forming a truncated cone-shaped macrocycle with a hydrophobic cavity and a hydrophilic outer surface. Depending on the number of glucose units, cyclodextrins are classified as α-, β-, and γ-CyD, where α, β, and γ denote the number of glucose molecules constituting CyD as 6, 7, and 8, respectively. As evidence of its broad recognition, CyD appeared in the 2015 National Center Test for University Admissions in Japan and has been featured in a column of a Japanese high school chemistry textbook (Noguchi, 2024). This tendency indicates the development of an educational context that promotes inquiry-based learning, allowing students to investigate topics such as the diversity of inclusion compounds as an integral component of digital learning in STEM (Science, Technology, Engineering, and Mathematics) education (Khalid et al., 2025).

Ferrocene (Fc) serves as a noteworthy molecule of an organometallic complex, characterized by the presence of metal-carbon bonds. For instance, it was selected in an entrance examination question at the Tokyo Institute of Technology (now Institute of Science Tokyo) in 2022. The author conducted a search for and reported on crystal structures of introductory organic compounds covered in high school chemistry. A case study has been documented in which its molecular structure, as determined by X-ray crystallographic analysis, was developed as a web-based educational resource, referred at Noguchi (2022). While this included cyclodextrin inclusion compounds such as *p*-phenylazophenol, ferrocene was not referred to. Ferrocene is insoluble in water and has a propensity to be readily incorporated within cyclodextrin. Reviews on encapsulation interactions in CyD inclusion complexes (e.g., Song et al., 2009), α-CyD encapsulates one molecule of Fc with two molecules of CyD, β-CyD encapsulates one molecule of Fc with one molecule of CyD, and γ-CyD encapsulates one molecule of Fc with one molecule of CyD in an orientation 90° different from that of β-CyD; i.e., 'Fc in CyD model', as demonstrated in Fig. 1.

However, upon reviewing the literature cited by Song et al. (2009), I found that it provided absolutely no support for this claim. This experience serves as a lesson that simply instructing students to “look it up” carries the risk of them encountering incorrect information. Therefore, in response to the question in the Japanese high school chemistry textbook – "Let's investigate what kinds of inclusion compounds exist" – and as part of a pilot project to develop STEM teaching materials for advanced learning about inclusion compounds, a preliminary investigation was conducted to determine whether any useful crystal structural data existed for CyD containing Fc.

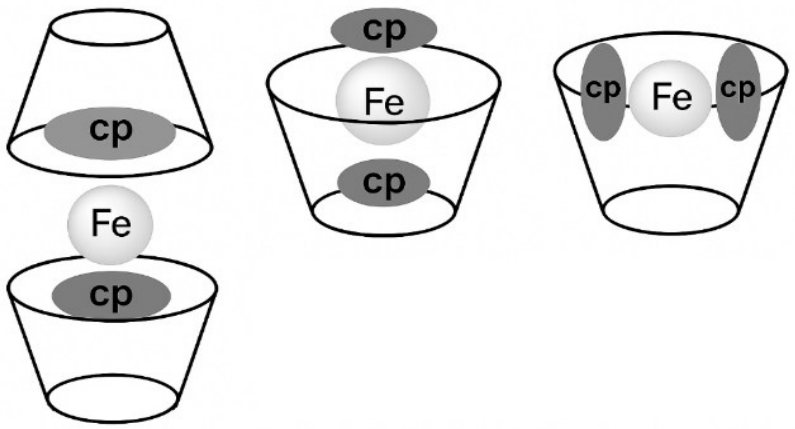

Fig. 1 'Fc in CyD model': From left to right, inclusion complexes of ferrocene ($Fe(cp)_2$) in α-, β-, and γ-Cyclodextrin, where cp denotes cyclopentadienyl anion, $C_5H_5^-$ (Song et al., 2009).

2. Materials and Methods

The search for crystal structural data was conducted using the Cambridge Crystallographic Data Centre (CCDC) website (https://www.ccdc.cam.ac.uk/structures/).

3. Results and Discussion

According to the author's search and critical literature review, the research article by Odagaki et al. (1990) is the first to report X-ray crystallographic analysis of an inclusion complex in which two molecules of α-CyD encapsulate one molecule of Fc (see Fig. 2). Fc is a redox active species and can be readily oxidized to Fc^+ by oxidizing agents. The crystal structure of α-CyD incorporating Fc^+ has been reported by Klingert & Rihs (1991) (see Fig. 3). While the inclusion state of Fc^+ resembles that of Fc, it is clear that the counterion, the hexafluorophosphate anion PF_6^-, is separated from CyD. This finding could serve as a starting point for further investigation into the inclusion of redox-active compounds in cyclodextrins.

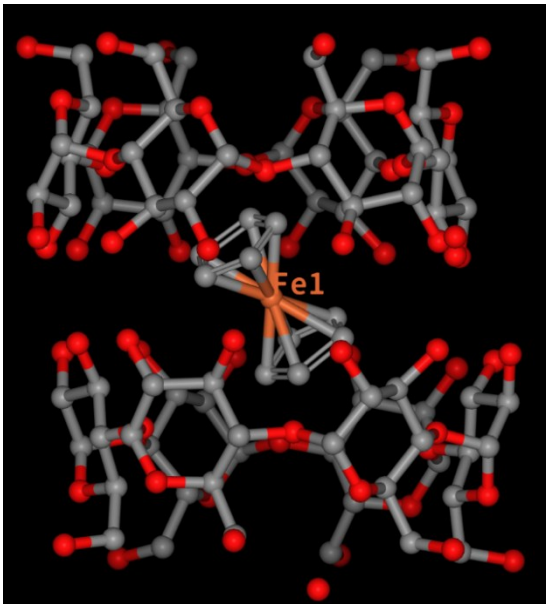

Fig. 2 Crystal structure of Fc in α-CyD (Odagaki et al., 1990).

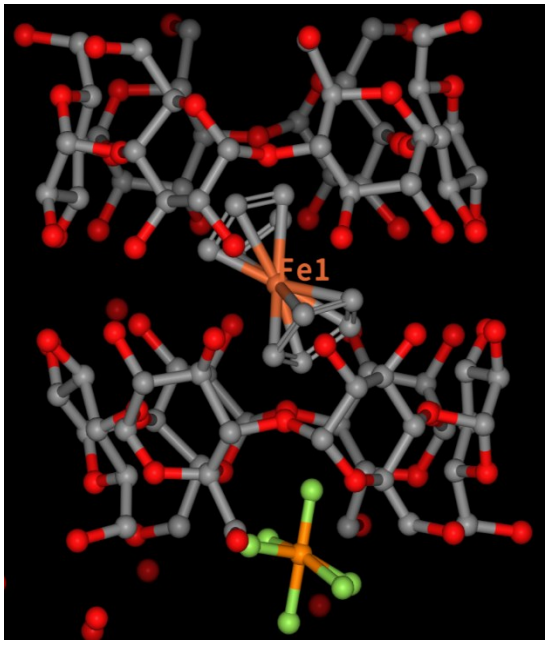

Fig. 3 Crystal structure of $FcPF_6$ in α-CyD (Klingert & Rihs, 1991).

Liu et al. (2005) reported an X-ray crystallographic analysis of a β-CyD–Fc complex with a stoichiometric ratio of β-CyD:Fc=4:5 (Fig. 4). On the other hand, however, to the best of my knowledge, no reports of X-ray crystallographic analysis of γ-CyD including Fc have been found. Although the 'Fc in CyD' model is concise and straightforward, it is founded to be obvious that the crystal structure data does not necessarily support it in every detail. Thus, is there anything other than the crystal structure data that supports the Fc in CyD model, especially in the case of γ-CyD? In a theoretical simulation of γ-CyD capturing Fc in the gas phase, the stabilization energies for Fc included in both the vertical and horizontal orientations were compared, and it was concluded that they possess essentially the same energy (Menger & Sherrod, 1988). The calculations also demonstrated that the ferrocene as guest and α-CyD as host within the 1:l complex, finding too little space to penetrate deeply, tilts 40-45° at the upper rim of the α-CyD cup. Furthermore, ^{13}C NMR measurements of powder samples suggest that Fc is inclusively bound to γ-CyD at a precession angle of 69° (Imashiro et al., 1992).

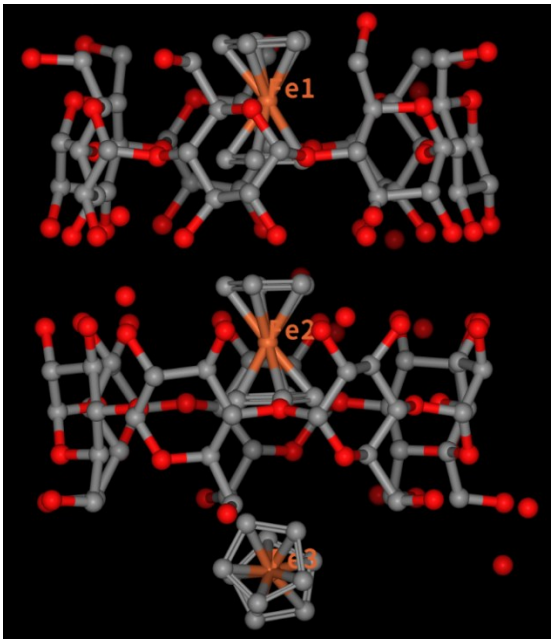

Fig. 4 Crystal structure of Fc in β-CyD (Liu et al., 2005).

The original 'Fc in CyD' model was proposed for the first time based on absorption and circular dichroism spectra of the complexes (Harada & Takahashi, 1984). Described above, the crystal structure of α-CyD–Fc (2:1) was reported by Odagaki et al. (1990) and in addition, β-CyD–Fc (4:5) was also reported (Liu et al., 2005). Subsequent reviews such as Hapiot et al. (2006) and Monflier et al. (2007) continue to cite the model proposed by Harada and Takahashi (1984), appearing to persist in disregarding the structure derived from crystallographic analyses (Liu et al., 2005; Odagaki et al., 1990) and theoretical calculation (Menger & Sherrod, 1988). Besides, Song et al. (2009) reviewed the 'Fc in CyD' model citing wrong references; it regrettably seems as though the 'Fc in CyD' model has been deified as an absolute truth. The 'Fc in CyD' model might be suitable for learning the sizes of CyD and Fc, and their manner of host-guest phenomena of inclusions for STEM education. However, there is little evidence to support precisely this 'Fc in CyD' model.

Are these crystal structural data useless in STEM education? Instead of the 'Fc in CyD' model based on uncertainty, the author proposes that the Fc/Fc^+ in α-CyD has potential effectiveness. Between Fc and Fc+, bond lengths are virtually indistinguishable from those of Fc (e.g., Tanabe et al., 2018). The interaction of Fc^+ and α-, β-, and γ-CyD in aqueous and D_2O solution are also studied

using ^{1}H NMR measurements (Moozyckine et al., 2001). This supplemental resource would be used for further study to develop STEM learning materials in the future.

4. Conclusion

Cyclodextrin (CyD) is a cyclic molecule with a hydrophobic cavity and hydrophilic exterior, making it useful for forming inclusion compounds and for inquiry-based STEM education. Ferrocene (Fc), an important organometallic compound, is commonly taught in higher education, but its inclusion compounds with CyD have not been well covered in educational materials. Although literature often states simple inclusion ratios (e.g., 2:1 for α-CyD, 1:1 for β- and γ-CyD), closer examination demonstrated limited or inconsistent supporting evidence. Verified crystal structures exist for α-CyD including Fc (2:1) and its oxidized form Fc^{+}, and for β-CyD with a more complex 4:5 ratio. However, no confirmed crystal structure exists for γ-CyD–Fc inclusion. The commonly cited "Fc in CyD model," based mainly on spectroscopic data, has been treated as definitive despite lacking strong confirmation from crystal structure studies and containing citation issues. While some experimental and theoretical evidence supports interaction between γ-CyD and Fc, it does not fully validate this Fc in CyD model. Therefore, the author recommends using the well-established Fc/Fc^{+}–α-CyD inclusion compounds in STEM education instead of the ambiguous Fc in CyD model, as they are better supported by reliable structural and experimental data.

5. Acknowledgements

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