Beta-cyclodextrin (CD) Inclusion Complexes of Disconnected Synthetic Cannabinoid Molecules

Ashley Bradbury, M. Rashidi Abdull Manap, Tasnim Munshi, Ian J. Scowen

School of Chemistry, University of Lincoln, Joseph Banks Laboratories, Green Lane, Lincoln, Lincolnshire, LN6 7DL, UK

INTRODUCTION

SERS has proven to be a powerful screening technique for synthetic cannabinoids.[1] Research shows successful capping of silver nanoparticles with thiolated CD for the detection of polycyclic aromatic hydrocarbons for SERS enhancement.[2] CD (figure 1) is an oligosaccharide composed of seven α-D-glucopyranoside units and is commonly used in pharmaceuticals[3] and drug delivery[4] as its cavity can be used to form inclusion complexes with hydrophobic molecules.

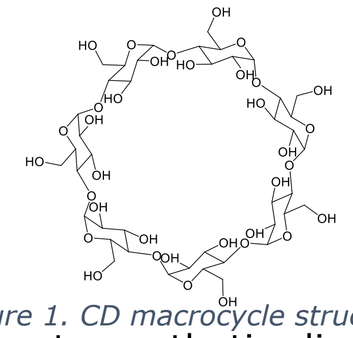

Figure 1. CD macrocycle structure.

With the use of the retrosynthetic disconnection theory (figure 2) we are able to predict the binding of the cannabinoid RCS-4 with CD for SERS enhancement. The molecules selected for study were 1-methylindole-3-carboxylic acid, methyl 1-methyl-1H-indole-3-carboxylate and 4-methoxyacetophenone. Down to the expensive nature of 1-pentyl indole-3-carboxylic acid, 1-methylindole-3-carboxylic acid is used as a replacement.

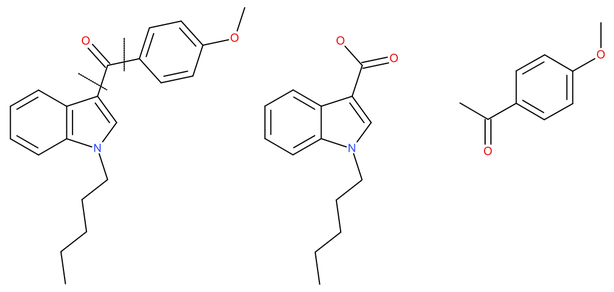

Figure 2. Disconnection theory for RCS-4 cannabinoid into 1-pentyl indole-3-carboxylic acid and 4-methoxyacetophenone.

EXPERIMENTAL

(1) Methylation of 1-methyl indole-3-carboylate

Due to possible hydrogen bonding effects with 1-methylindole-3-carboxylic acid and CD hydroxyl groups we decided to study the complexation with methyl 1-methyl-1H-indole-3-carboxylate. To obtain this material we methylated 1-methyl indole-3-carboxylate using an established method (figure 3).[5] Results were validated with computational calculations.

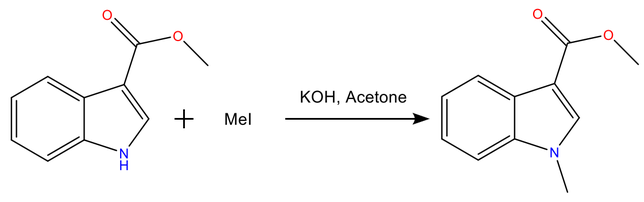

Figure 3. Synthesis of methyl 1-methyl-1H-indole-3-carboxylate by the methylation of methyl indole-3-carboxylate.

(2) Formation of Inclusion Complexes

Methods for forming inclusion complexes were adapted from an established method.[6]

Complex 1: **0.5 mmol** CD + **0.5 mmol** methyl 1-methyl-1H-indole-3-carboxylate

Complex 2: **0.5 mmol** CD + **0.5 mmol** 1-methylindole-3-carboxylic acid

Complex 3: **0.5 mmol** CD + **0.5 mmol** 4-methoxyacetophenone

Compounds were dissolved in hot solvent (water:methanol, 75:25) and stirred for 1 hour before taking samples for Raman and IR analysis.

(3) Thiolation of CD

This two-step synthetic strategy was obtained from an established method (figure 4).[7]

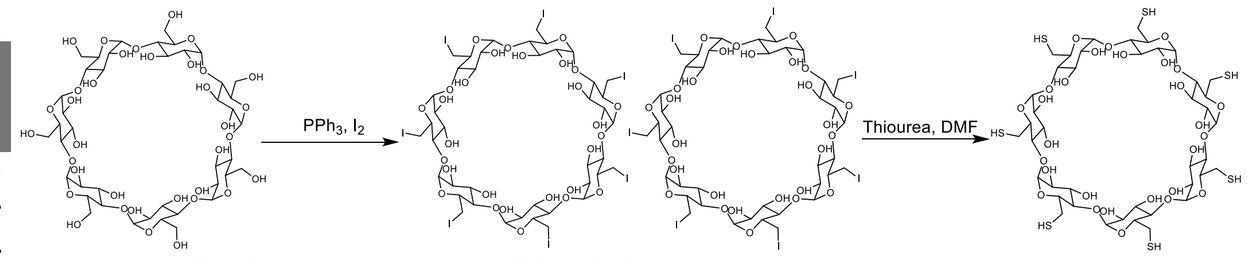

Figure 4. Synthesis of iodinated CD with triphenylphosphene and iodine, followed by the thiolation with thiourea and DMF.

RESULTS AND DISCUSSION

(1) Methylation Results

Computational vibrational data was obtained for methyl 1-methyl-1H-indole-3-carboxylate using Gaussian methods. Vibrational data confirmed the formation of the product by comparison of computational vibrational data with experimental IR and Raman data. The structure of the methylated indole in the gas phase was optimized using DFT and HF methods (figure 5).

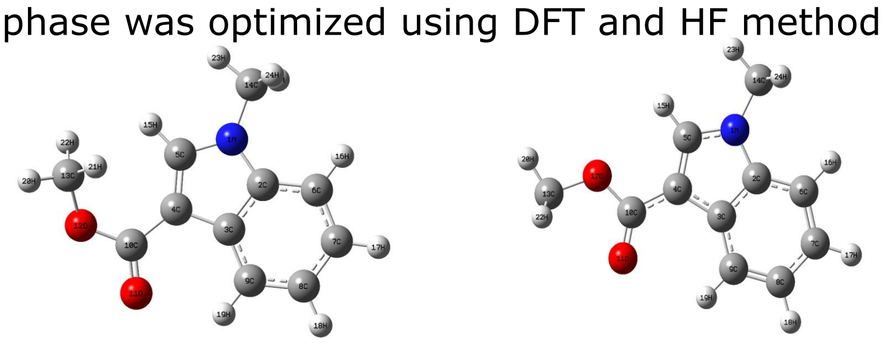

Figure 5. DFT (left) and HF (right).

(2) Complexation analysis of Complex 1

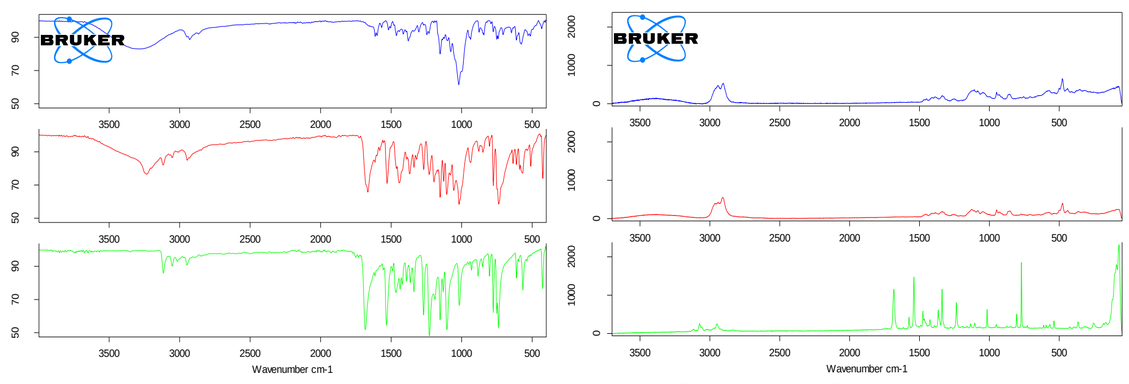

Figure 6. IR and Raman experimental spectra. CD (blue). CD and Methyl 1-methyl-1H-indole-3-carboxylate complex (red). Methyl 1-methyl-1H-indole-3-carboxylate (green).

IR and Raman data (figure 6) show significant shift and change in peak shape of the OH and C=O peaks, both show a significant decrease in wavenumber, indicating hydrogen bonding of the OH with the carbonyl group of Methyl 1-methyl-1H-indole-3-carboxylate.

CONCLUSION

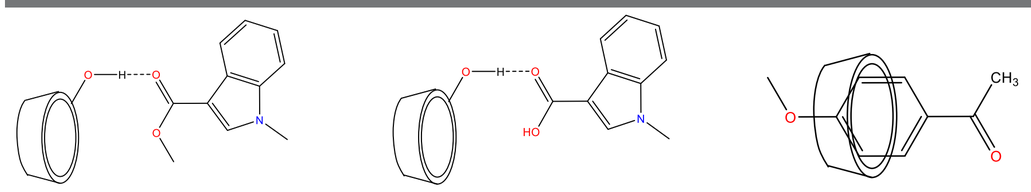

Figure 7. Complex 1 (left). Complex 2 (middle). Complex 3 (right).

From the experimental data obtained it is predicted that CD shows interaction with the molecules (figure 6). Hydrogen bonding of the carbonyl groups prevents inclusion of Methyl 1-methyl-1H-indole-3-carboxylate and 1-methylindole-3-carboxylic acid whilst acetophenone is small enough to enter the cavity with no hindrance from hydrogen bonding. From this data we are able to predict the binding of cannabinoid RCS-4 with CD (figure 7).

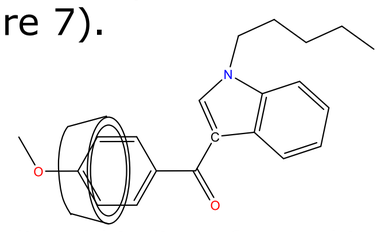

Figure 7. Predicted binding of cannabinoid RCS-4 with CD.

ACKNOWLEDGMENTS

With thanks to Nabila and Steve for spectroscopic analysis.

REFERENCES

[1] T. Mostowtt and B. McCord, *Talanta*, 2017, 164, 396–402.
[2] Y. Xie, X. Wang, X. Han, X. Xue, W. Ji, Z. Qi, J. Liu, B. Zhao and Y. Ozaki, *Analyst*, 2010, 1389–1394.
[3] S. Menuel, J.-P. Joly, B. Courcot, J. Elysée, N.-E. Ghermani and A. Marsura, *Tetrahedron*, 2007, 63, 1706–1714.
[4] T. R. Thatiparti, A. J. Shoffstall and H. A. von Recum, *Biomaterials*, 2010, 31, 2335–47.
[5] A. Schäfer, E. S. Burstein and R. Olsson, *Bioorg. Med. Chem. Lett.*, 2014, 24, 1944–1947.
[6] S. E. Williams, Modifying Hydrogen Bonding Environments with Novel Rotaxanes Derived From Heteromolecular Organic Assemblies, 2013.
[7] M. T. Rojas, R. Kiiniger, J. F. Stoddart and A. E. Kaifer, J. Am. Chem. SOC, 1995, 117, 336–343.

UNIVERSITY OF LINCOLN