Study of the Binding Interaction between β-Cyclodextrin and Carbendazim using Nuclear Magnetic Resonance Chemical Shift Titrations

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Introduction

- Cyclodextrins (CDs) are cyclic oligosaccharides containing glucopyranose units.[1] They are used in foods and pharmaceuticals due to their remarkable encapsulation properties that lead to a "host-guest" type relationship.[2]
- β-CD is composed of 7 glucose units. The hydrophobic character of the cavity formed allows the dissolution of compounds with low solubility. (Figure 1).
- Carbendazim (MBC) is a benzimidazole fungicide and a metabolite of benomyl used as a casting worm control agent. (Figure 2) Studies have found high doses of carbendazim cause infertility to laboratory animals.[3]
- The ability of β-CD to form an inclusion complex with MBC represents an improvement of the solubility and the fungicidal activity of carbendazim. Hence, β-CD could be used as a molecular vehicle to transport MBC more efficiently.[4]

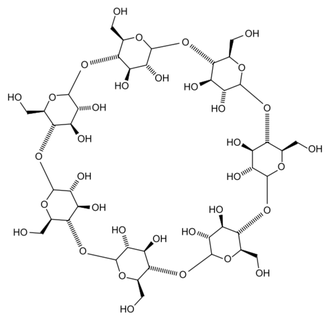

Figure 1. Structure of β-cyclodextrin

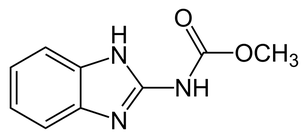

Figure 2. Structure of carbendazim

Objectives

- Quantify the strength of the interaction between β-CD and MBC using ^{1}H-NMR chemical shift titrations using deuterated dimethyl sulfoxide (DMSO-d_6) as a solvent.
- Determine the binding constants (K_a) applying the Rose-Drago method and compare the values to those obtained by other analytical methods.
- Demonstrate the efficiency of the chemical shift titration technique and optimize the analytical method.

References

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3. Aire, T. A. Short-term effects of carbendazim on the gross and microscopic features of the testes of Japanese quails (Coturnix coturnix japonica). *Anatomy and Embryology,* **2005**, *210,* 43–49
4. Ge, X.; Huang, Z.; Tian, S.; Huang, Y.; Zeng, C. Complexation of carbendazim with hydroxypropyl-β-cyclodextrin to improve solubility and fungicidal activity. *Carbohydrate Polymers.* **2012**, *89, 208–212*

Experimental

NMR Spectroscopy

- Nuclear Magnetic Resonance Spectroscopy is an analytical technique used to obtain structural information about molecules by perturbing nuclear spin. It is generally faster than other analytical techniques, because it does not require sample derivatization or separation.

Chemical Shift Titrations

- Chemical shift (ppm) is determined as a function of concentration since it changes when the host molecule (HM) interacts in the guest molecule (GM).
- By analyzing the change in chemical shift (Δδ) of β-CD and MBC for the free and complexed states, NMR can allow the determination of the binding strength between the host and guest molecules.

Methodology

- β-CD acts as a host molecule and MBC acts as a guest molecule.
- Stock solutions 2.89 mM and 0.123 M were prepared for the HM and GM, respectively.
- 400 µL of β-CD were added to an NMR tube and aliquots of MBC are added to the tube according to Table 1 to increase $[G]_t/[H]_t$ ratio from 0 to 80.
- After each addition of GM, the solution was analyzed using ^{1}H-NMR spectroscopy.
- Chemical shift for each hydrogen is determined and tabulated to determine Δδ as a function of concentration.

Added amount of GM solution (µL)	Integrated amount of GM solution (µL)	$[G]_t/[H]_t$ ratio
0.00	0.00	0
5.60	5.60	0.6
3.80	9.40	1.0
15.0	24.40	2.6
28.0	52.40	5.6
40.0	92.40	9.8
70.0	162.40	17.2
140	302.40	32.1
200	502.40	53.3
250	752.40	79.8

Table 1. Composition of the ten different solutions analyzed using ^{1}H-NMR spectroscopy.

Acknowledgements

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Results and Discussion

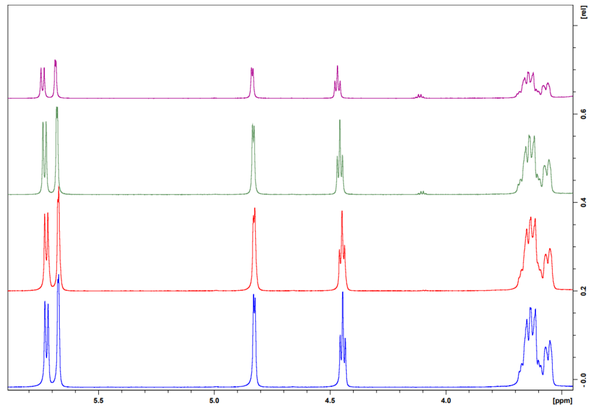

Figure 3. Downfield migration of hydrogens due to complex formation.

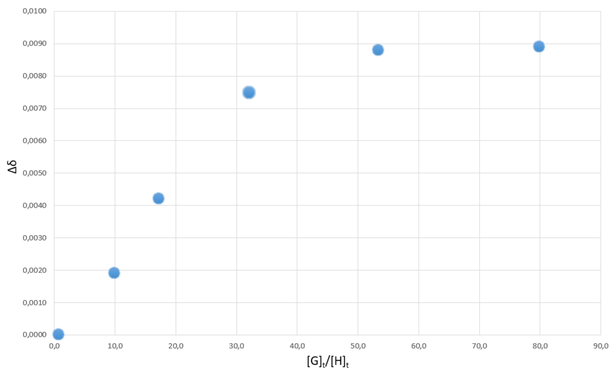

Figure 4. Non-linear least-squared relationship between chemical shift and $[G]_t/[H]_t$ ratio.

- The stoichiometry of interaction between β-CD and MBC was not determined. The hydrophobic cavity of β-CD is also able to host DMSO-d_6 molecules, hence it competes with carbendazim. It was assumed to be 1:1.
- SigmaPlot software was used to perform a on-linear graphical analysis to determine the binding constant applying the Rose-Drago method.
- The apparent calculated value for the binding constant was 0.0266 M^{-1} indicating a weak bonding between the HM and the GM.

Future Work

- Optimize the analytical method by finding a solvent that has a higher solubility of carbendazim.
- Apply the method to other benzimidazoles such as fuberidazole or thiabendazole to demonstrate its efficiency.