



FROM POLYMERS TO PORPHYRINS: SUPRAMOLECULAR CONTROL ASSERTED BY CYCLODEXTRIN OLIGOMERS

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Thesis submitted for the degree of
Doctor of Philosophy
in
the University of Adelaide
School of Chemistry and Physics

January, 2016

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ABSTRACT

Cyclodextrin oligomers are non-toxic and biodegradable hosts for a wide array of potential guest molecules. Consequently, they are currently being used in a range of applications for small molecule and polymer-based drug delivery systems. As it stands, the majority of these oligomer systems are derived from α - and β -cyclodextrin. However, cyclodextrin oligomers derived from γ -cyclodextrin are relatively unknown. Oligomer systems derived from γ -cyclodextrins may have the capability to form stable host-guest complexes with larger drug targets such as porphyrins. In order to develop applications for these new γ -cyclodextrin oligomer systems fundamental studies on their host-guest complexes must be performed. A literature review on cyclodextrins as supramolecular hosts as well as some key guest molecules and applications are outlined in Chapter 1.

Chapter 2 investigates the complexation of a known photosensitiser, 5,10,15,20-tetra(*p*-sulfonatophenyl)porphyrinate, H_2TSPP^{4-} , with γ -CD and five of its modified oligomers in aqueous solutions. Two previously reported succinimide-linked γ -CD dimers (33 γ -CD₂suc and 66 γ -CD₂suc) were prepared as well as two new oxalate-linked γ -CD dimers (33 γ -CD₂ox and 66 γ -CD₂ox) and a novel benzene linked γ -CD trimer (666 γ -CD₃bz). The host-guest complexation of H_2TSPP^{4-} by the cyclodextrin hosts was investigated by 2D ¹H NOESY NMR, variable temperature UV-Vis spectroscopy and molecular modelling. The experiments are designed to investigate the effects of the cyclodextrin oligomer subunit orientation (3,3-, 6,6- or 6,6,6-) as well as the variation in length of the covalent bridge. Additionally, the study is intended to give insight into the various host-guest complexes and complex conformers in the H_2TSPP^{4-} . γ -CD oligomer equilibria.

Chapter 3 investigates the host-guest complexation of a less water-soluble porphyrin, 5,10,15,20-tetra(*p*-carboxyphenyl)porphyrinate, H_2TCPP with γ -CD and its oligomers. The

complexation of H_2TCPP in its multiply ionised states $H_3TCPP^{3-}/H_2TCPP^{4-}$ by native γ -CD, 33γ -CD₂suc, 66γ -CD₂suc, 33γ -CD₂ox, 66γ -CD₂ox and 666γ -CD₃bz was investigated by 2D ¹H NOESY NMR spectroscopy, UV-Vis spectroscopy and molecular modelling. The experiments are designed to investigate the effects the ionic porphyrin substituents, porphyrin aggregation and the cyclodextrin oligomer subunit orientation (3,3-, 6,6- or 6,6,6-) as well as the variation in length of the covalent bridge on the host-guest complexation of $H_3TCPP^{3-}/H_2TCPP^{4-}$ by the cyclodextrin hosts.

In Chapter 4, a 3% randomly substituted sodium 5-(*p*- β -alanylaminophenyl)-10,15,20-tris(*p*-sulfonatophenyl)-porphyrin poly(acrylate) (PAATSPPal) was prepared. The complexation of the polymer substituents of PAATSPPal (TSPPal) by native γ -CD, 33γ -CD₂suc, 66γ -CD₂suc, 33γ -CD₂ox, 66γ -CD₂ox and 666γ -CD₃bz was investigated by 2D ¹H NOESY NMR spectroscopy, variable temperature UV-Vis spectroscopy and rheology. The experiments were designed to give insight into the effects of the different cyclodextrin hosts on the relative strengths of host-guest complexation and the formation of inter-strand poly(acrylate) cross-links in forming photoactive hydrogels.

In Chapter 5, PAA was 3 % randomly substituted with 1- or 2- modified naphthalene to give isomeric poly(acrylate)s PAA1NSen, PAA1NShn, PAA2NSen and PAA2NShn, respectively. The complexation of the polymer substituents by native β -CD or γ -CD and four succinamide-linked cyclodextrin dimers (33β -CD₂suc, 66β -CD₂suc, 33γ -CD₂suc and 66γ -CD₂suc) was investigated by 2D ¹H NOESY NMR spectroscopy, fluorescence spectroscopy and rheology. The experiments are designed to give insight into the effects of naphthyl substitution position, the length of the tether attaching the naphthalene substituent to the poly(acrylate) back-bone and the size and geometry of the cyclodextrin hosts. These factors are expected to determine the relative strengths of host-guest complexation and the formation of inter-strand poly(acrylate) cross-links to form hydrogels.

Chapter 6 describes the experimental methodology employed in these studies. The information in this thesis hopes to provide greater insight into the formation of γ -CD oligomer host-guest complexes and may lead to the better design of drug delivery systems, host-guest polymer networks and intrinsically therapeutic hydrogels.

DECLARATION

This is to declare that the work presented within this thesis is original and was carried out at the University of Adelaide during the period of 2010-2015. This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is given.

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/ / 2016

ACKNOWLEDGMENTS

This thesis would not have been written without the help of many people that supported me throughout my candidature. First and foremost I would like to thank Prof. Stephen Lincoln for allowing me to undertake a Ph.D. under his tutelage. I will be forever grateful for your insightful advice (in and out of the laboratory), Cold War history lessons, guidance, eye for detail and most of all patience. Thank you for always being a dedicated supervisor from the start of my honours year to the end of this project. Moreover, I would like to thank my second supervisor, Assoc. Prof. Tak Kee, for his collaboration, advice, support and passionate conversations about physical chemistry.

To Dr. Duc Truc Pham you are a true friend and someone I will always look up to. Without your help and mentoring I would have never been able to finish this project. Noby, thank you for friendship, numerous rounds of proof reading, hours of conversation, travel and food advice and your wonderful singing voice (every time I hear *Save the Best for Last* I will think of you). To my weekend lab friend Liang, thank you for always asking if I have had lunch, letting me into the building when I have forgotten my card, helping me with maths and patiently translating numerous Chinese restaurant menus. I would also like to thank Mitch and Tien with their help, friendship and collaboration at the early stages of this project. Furthermore, I would like to thank all of Lincoln and Kee group members I have worked with throughout the years and in particular Hilary (H-bomb), Jianjia, Mandy, Scott, Taka and Trang for their help, support and friendship.

I would like to thank Prof. Xuhong Guo, Dr. Jie Wang and Yiming Wang of East China University of Science and Technology for their collaboration and rheological measurements.

Furthermore, I would like to thank the research groups of Prof. Christopher Easton of the Australian National University and Prof. Robert Prud'homme of Princeton University for their collaboration.

I would like to thank the entire Chemistry Department of The University of Adelaide for their friendship and support. I would like to thank Phil Clements for all of his hard work on all things NMR related in this work. Thank you for all of the reprints, shimming advice and your good taste in music. Gino, thank you for always looking out for me in and out of the teaching laboratory and providing me with employment in the hardest of financial times. Your stories on “the good old days at Adelaide Uni” and advice on high risk superannuation will never be forgotten.

I would like to thank my Mother, Decima, and Father, David, for the love and support they have provided my entire life. Mum, thank you always knowing what I need, even when I don't know myself sometimes. Dad, thank you for teaching me the tenacity needed to continue through the toughest times in life, for always answering the phone (sometimes whilst flying) and for always trying to solve my problems even when you can't. I would like to thank my surrogate mother Iwona, thank you for everything you do (pickups, drop offs, cakes, holidays) and for treating me like one of your own. I would like to thank my all of my friends, and in particular, Fozz, Michael, Tom, and Lachie. Thank you for providing weekend distractions (Michael for the Fortress of Solitude), tales from Naracoorte High and putting life into perspective from time to time. I would like to thank my sister Kristie for being an amazing roommate, sibling and friend. Thank you for lending me the car, picking up my socks, buying the toilet paper and looking after me from the day I was born (except for that time you dropped me on my head).

Finally, I would like to thank my dearest Karolina, we did it. This thesis is as much yours as it is mine as I would have never finished it without meeting you. Thank you for being the love of my life, my best friend, my partner and my Chimlick. I cannot put into words the gratitude I feel towards how much you have changed my life or how much I love you so I'll end it here.

ABBREVIATIONS

1. General

Å	angstrom (10^{-10} m)
Ar	aryl
d	Density (g cm^{-3})
δ	chemical shift (ppm)
ΔG	Gibbs free energy change
ΔH	enthalpy change
ΔS	entropy change
ε	molar absorptivity ($\text{mol}^{-1} \text{dm}^{-3} \text{cm}^{-1}$)
E	heat of formation (kJ mol^{-1})
FL	fluorescence spectroscopy
<i>et al.</i>	et alia
GC-MS	gas chromatography- mass spectrometry
Hz	Hertz
HPLC	high-performance liquid chromatography
I	ionic strength (mol dm^{-3})
I_F	fluorescence intensity
J	coupling constant (Hz)
K	stability constant ($\text{dm}^{-3} \text{mol}^{-1}$)
K_a	acid dissociation constant
K_{11}	stability constant for 1:1 host-guest complexes ($\text{dm}^{-3} \text{mol}^{-1}$)
K_{21}	stability constant for 2:1 host-guest complexes ($\text{dm}^{-3} \text{mol}^{-1}$)
K_D	dimerisation constant
m/z	mass/charge ratio

MS	mass spectrometry
MALDI TOF	matrix-assisted laser desorption-ionisation time-of-flight
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
PDT	photodynamic therapy
pH	$-\log[\text{H}^+]$
pKa	$-\log[K_a]$
ppm	parts per million
PS	photosensitiser
R_f	retention factor
R_c	relative retention factor to native cyclodextrins (in TLC)
T	temperature (K)
TLC	thin-layer chromatography
UV-Vis	ultraviolet-visible
wt	weight

2. Chemicals

α -, β -, γ -CD	α -, β -, γ -cyclodextrin
33 β -CD ₂ suc succinamide	<i>N,N'</i> -Bis((2 ^A S,3 ^A S)-3 ^A -deoxy- β -cyclodextrin-3 ^A -yl)
66 β -CD ₂ suc	<i>N,N'</i> -bis(6 ^A -deoxy- β -cyclodextrin-6 ^A -yl) succinamide
C18	octadecyl
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCM	dichloromethane

DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
en	1,2-diaminoethane
33 γ -CD ₂ ox	<i>N,N'</i> -Bis((2 ^A S,3 ^A S)-3 ^A -deoxy- γ -cyclodextrin-3 ^A -yl) oxalamide
66 γ -CD ₂ ox	<i>N,N'</i> -Bis(6 ^A -deoxy- γ -cyclodextrin-6 ^A -yl) oxalamide
33 γ -CD ₂ suc	<i>N,N'</i> -Bis((2 ^A S,3 ^A S)-3 ^A -deoxy- γ -cyclodextrin-3 ^A -yl) succinamide
66 γ -CD ₂ suc	<i>N,N'</i> -Bis(6 ^A -deoxy- γ -cyclodextrin-6 ^A -yl) succinamide
666 γ -CD ₃ bz	1,3,5- <i>N,N,N</i> -tris(6 ^A -deoxy-6 ^A - γ -cyclodextrin)-benzene
hn	1,6-diaminohexane
HP	hydroxypropyl
TCPP	5,10,15,20-tetra(<i>p</i> -carboxyphenyl)porphyrin
TSPP	5,10,15,20-tetra(<i>p</i> -sulfonatophenyl)porphyrin
NMP	<i>N</i> -methylpyrrolidin-2-one
1NSen	<i>N</i> -(2-aminoethyl)-1-naphthyl-sulfonamide
1NShn	<i>N</i> -(6-aminohexyl)-1-naphthyl-sulfonamide
2NSen	<i>N</i> -(2-aminoethyl)-2-naphthyl-sulfonamide
2NShn	<i>N</i> -(6-aminohexyl)-2-naphthyl-sulfonamide
PAA	poly(acrylate)
PAA1NSen	3% randomly 1NSen substituted PAA
PAA1NShn	3% randomly 1NShn substituted PAA
PAA2NSen	3% randomly 2NSen substituted PAA
PAA2NShn	3% randomly 2NShn substituted PAA
PAATSPPal	3% randomly TSPPala substituted PAA

PAM	poly(acrylamide)
TSPPala	5-(<i>p</i> - β -alanylaminophenyl)-10,15,20-tris(<i>p</i> -sulfonatophenyl)- porphyrin
TFA	trifluoroacetic acid
THF	tetrahydrofuran