FROM POLYMERS TO PORPHYRINS: SUPRAMOLECULAR CONTROL ASSERTED BY CYCLODEXTRIN OLIGOMERS

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CONTENTS

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 (33γ-CD_2suc and 66γ-CD_2suc) were prepared as well as two new oxalate-linked γ-CD dimers (33γ-CD_2ox and 66γ-CD_2ox) and a novel benzene linked γ-CD trimer (666γ-CD_3bz). The host-guest complexation of H_2TSPP^{4-} by the cyclodextrin hosts was investigated by 2D ^{1}H 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-CD_2suc, 66γ-CD_2suc, 33γ-CD_2ox, 66γ-CD_2ox and 666γ-CD_3bz was investigated by 2D ^{1}H 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) (PAATSPPala) was prepared. The complexation of the polymer substituents of PAATSPPala (TSPPala) by native γ-CD, 33γ-CD_2suc, 66γ-CD_2suc, 33γ-CD_2ox, 66γ-CD_2ox and 666γ-CD_3bz was investigated by 2D ^{1}H 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-CD_2suc, 66β-CD_2suc, 33γ-CD_2suc and 66γ-CD_2suc) was investigated by 2D ^{1}H 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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ABBREVIATIONS

1. General

Å	angstrom (10^{-10} m)
Ar	aryl
d	Density (g cm^{-3})
δ	chemical shift (ppm)
Δ*G*	Gibbs free energy change
Δ*H*	enthalpy change
Δ*S*	entropy change
ε	molar absorptivity (mol^{-1} dm^{-3} cm^{-1})
E	heat of formation (kJ mol^{-1})
FL	fluorescence spectroscopy
et al.	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 (dm^{-3} mol^{-1})
K_a	acid dissociation constant
K_{11}	stability constant for 1:1 host-guest complexes (dm^{-3} mol^{-1})
K_{21}	stability constant for 2:1 host-guest complexes (dm^{-3} 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	$-\log[H^+]$
p*K*a	$-\log[K_a]$
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
33β-CD_2suc	*N*,*N*′-Bis((2^{A}S,3^{A}S)-3^A-deoxy-β-cyclodextrin-3^A-yl) succinamide
66β-CD_2suc	*N*,*N*′-bis(6^A-deoxy-β-cyclodextrin-6^A-yl) succinamide
C18	octadecyl
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane

DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
en	1,2-diaminoethane
33γ-CD_2ox	*N*,*N*′-Bis((2^{A}S,3^{A}S)-3^A-deoxy-γ-cyclodextrin-3^A-yl) oxalamide
66γ-CD_2ox	*N*,*N*′-Bis(6^A-deoxy-γ-cyclodextrin-6^A-yl) oxalamide
33γ-CD_2suc	*N*,*N*′-Bis((2^{A}S,3^{A}S)-3^A-deoxy-γ-cyclodextrin-3^A-yl) succinamide
66γ-CD_2suc	*N*,*N*′-Bis(6^A-deoxy-γ-cyclodextrin-6^A-yl) succinamide
666γ-CD_3bz	1,3,5-*N*,*N*,*N*-tris(6^A-deoxy-6^A-γ-cyclodextrin)-benzene
hn	1,6-diaminohexane
HP	hydroxypropyl
TCPP	5,10,15,20-tetra(*p*-carboxyphenyl)porphyrin
TSPP	5,10,15,20-tetra(*p*-sulfonatophenyl)porphyrin
NMP	*N*-methylpyrrolidin-2-one
1NSen	*N*-(2-aminoethyl)-1-naphthyl-sulfonamide
1NShn	*N*-(6-aminohexyl)-1-naphthyl-sulfonamide
2NSen	*N*-(2-aminoethyl)-2-naphthyl-sulfonamide
2NShn	*N*-(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
PAATSPPala	3% randomly TSPPala substituted PAA

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