



**LINKED BETA-CYCLODEXTRIN TRIMERS:
From Molecular Recognition to
Polymer Network Hydrogels**

Hanh-Trang Nguyen
(Nguyễn Thị Hạnh Trang)

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ABSTRACT

The thesis describes the construction and characterisation of a variety of polymer network hydrogels based on β -cyclodextrin (β -CD) trimers and modified poly(acrylate)s.

Chapter 1 extensively reviews in cyclodextrin (CD) fields from its history from beginning in 1981 until 2013. The most significant work is highlighted as well as the field of polymer hydrogel, including the novel field of CD based polymer hydrogel.

In Chapter 2, a UV-vis and ^1H NMR spectroscopic study of the host-guest complexation by β -cyclodextrin (β -CD), 1,3,5-*N,N,N*-tris-(6^A-deoxy-6^A- β -cyclodextrin)-benzene (β -CD₃bz), and 1,3,5-*N,N,N*-tris(6^A-(2-aminoethyl)amino-6^A-deoxy-6^A- β -cyclodextrin)-benzene (β -CDen₃bz) of cationic crystal violet (CV^+) and pyronine B (PB^+) and zwitterionic rhodamine B (RB) in aqueous phosphate buffer at pH 7.0 and $I = 0.10 \text{ mol dm}^{-3}$ is described. The complexation constants and the associated ΔH_{11} and $T\Delta S_{11}$ for all nine complexes coincide with an entropy-enthalpy compensation plot for the formation of a wide range of β -CD and modified β -CD host-guest complexes reported in the literature. Crystal violet also forms $(\beta\text{-CD})_2.\text{CV}^+$, $(\beta\text{-CD}_3\text{bz})_2.\text{CV}^+$ and $(\beta\text{-CDen}_3\text{bz})_2.\text{CV}^+$ complexes characterized by $10^{-2}K_{21}$ (298.2 K) = 2.14, 4.57 and 3.86 $\text{dm}^3 \text{ mol}^{-1}$ and analogous $(\beta\text{-CD})_2.\text{PB}^+$, $(\beta\text{-CDen}_3\text{bz})_2.\text{PB}^+$ and $(\beta\text{-CDen}_3\text{bz})_2.\text{RB}$ complexes also form, but the $(\beta\text{-CD}_3\text{bz})_2.\text{PB}^+$, $(\beta\text{-CD})_2.\text{RB}$, and $(\beta\text{-CD}_3\text{bz})_2.\text{RB}$ complexes were not detected. The effects of the structures of the hosts and guests on the complexation processes are discussed.

In Chapter 3 the characterisation stability of constants and thermodynamic patterns in polymer hydrogels based on host-guest complexation of the linked β -CD trimers with the dodecyl (C12) and octadecyl (C18) 3% randomly substituted poly(acrylate)s PAAC12 and PAAC18 in aqueous solution are discussed. These studies compare hydrophobic interactions of the C12 and C18 substituted poly(acrylate)s and their interaction with β -CD and linked β -CD trimers. The complexation processes were studied by 2D NOESY ^1H NMR spectroscopy, ITC, dynamic light scattering and rheology. These data are used to establish the extent to which these interactions influence hydrogel formation in more concentrated solutions.

In Chapter 4 the supramolecular chemistry of polymer hydrogel based on host-guest chemistry of the linked β -cyclodextrin trimers and four adamantyl substituted

poly(acrylate)s with different linker tether lengths is discussed. 2D NOESY ^1H NMR spectroscopy, isothermal titration calorimetry and rheological studies show that the β -CD groups of the two linked β -cyclodextrin trimers, β -CD₃bz and β -CDen₃bz, complex the adamantyl substituents and their tethers in 3.0% substituted poly(acrylate)s to form intra- and inter-poly(acrylate)s strand cross-links in aqueous solution. The structures of the linked- β -cyclodextrin trimers and the length of the tether between the adamantyl substituent and the poly(acrylate)s backbone have substantial effects on the complexation constants, K_{11} , and the associated thermodynamic parameters. This is partially shown for the complexation by β -CD₃bz of the adamantyl substituents as tether length varies from -CONH- (3.45×10^4) through -CONH(CH₂)_nNHCO- where $n = 2$ (2.09×10^5), 6 (3.17×10^5) or 12 (7.46×10^4) in 0.13 – 0.37 wt.% substituted poly(acrylate)s solutions and the figures in brackets are the K_{11} in $\text{dm}^3 \text{mol}^{-1}$ at 298.2 K. For the same sequence of substituted poly(acrylate)s the variation of viscosity is: 0.03, 3.78, 3.48, and 2.03 Pa s^{-1} at 500 s^{-1} shear rate at 298.2 K for 5.0 wt.% substituted poly(acrylate)s solutions in which the β -CD groups of β -CD₃bz and the adamantyl substituents are equimolar at $1.5 \times 10^{-2} \text{mol dm}^{-3}$. The eight data sets for the β -CD₃bz and β -CDen₃bz systems are discussed in terms of host-guest interactions between the host β -CD groups and the guest adamantyl substituents of the substituted poly(acrylate)s and are compared with those for the analogous β -CD systems.

In chapter 5, the supramolecular chemistry of the poly(acrylate)s hydrogels based on host-guest complexations of the linked β -CD₃bz and β -CDen₃bz trimers with the dansyl substituent guests (DS) attached through tethers of three different lengths containing 2, 6 and 12 methylene groups in 3.0 % randomly substituted, PAADSen, PAADShn and PAADSddn are discussed. The six systems have been characterized at the molecular level by 2D NOESY ^1H NMR, isothermal titration calorimetry, fluorescence spectroscopy and time-resolved fluorescence, and at the macroscopic level by dynamic light scattering and rheology. The data gathered are consistent with individual dansyl substituents forming aggregates and being complexed by the linked β -CD₃bz and β -CDen₃bz trimers in within poly(acrylate)s strands in dilute solutions and between poly(acrylate)s strands in hydrogels. The trends in β -CD₃bz and β -CDen₃bz complex stability constants fluorescence life times and viscosities of six systems are discussed.

Chapter 6 describes the experimental methodology deployed in the study.

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 2010-2013. 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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PUBLICATIONS AND PRESENTATIONS

Journal Articles:

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- **Nguyen, Hanh-Trang;** Pham, Duc-Truc; Lincoln, Stephen Frederick; Wang, Jie; Guo, Xuhong; Easton, Christopher J.; Prud'homme, Robert K. Host–Guest Chemistry of Linked β -Cyclodextrin Trimers and Adamantyl Substituted Poly(acrylate)s in Aqueous Solution. *Polymer Chemistry*, **2013**, 4(3), 820-829. DOI: 10.1039/C2PY20746J
- **Nguyen, Hanh-Trang;** Pham, Duc-Truc; Lincoln, Stephen Frederick; Wang, Jie; Guo, Xuhong; Easton, Christopher J.; Prud'homme, Robert K. Complexation of Hydrophobe Substituted Poly(acrylate)s by β -Cyclodextrin Dimers and Trimers in Aqueous Solution and Hydrogels. *Ready to submit*, **2013**.

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- Pham, Duc-Truc; **Nguyen, Hanh-Trang;** Lincoln, Stephen Frederick; Wang, Jie; Guo, Xuhong; Easton, Christopher J. Beta-Cyclodextrin Trimers and Adamantyl Substituted Polyacrylate Network: Synthesis and Characterization. *19th International Conference on Organic Synthesis*. Melbourne, Australia, July 1-6, 2012.
- **Nguyen, Hanh-Trang;** Pham, Duc-Truc; Lincoln, Stephen Frederick; Wang, Jie; Guo, Xuhong; Easton, Christopher J.; Prud'homme, Robert K. Supramolecular Chemistry of Beta-Cyclodextrin Trimers and Adamantyl Substituted Polyacrylates. *16th International Cyclodextrin Symposium*. Tianjin, China 6-10 May, 2012: pp.II-01.

- **Nguyen, Hanh-Trang;** Pham, Duc-Truc; Wang, Jie; Guo, Xuhong; Lincoln, Stephen Frederick; Easton, Christopher J. Synthesis of β -cyclodextrin trimers for novel polymer networks. *Asian Cyclodextrin Conference* (6th: 2011: Canberra, Australia) ACC2011

ABBREVIATIONS

1. General

Å	ångström (10^{-10} m)
Ar	aryl
d	Density (g cm^{-3})
δ	chemical shift (ppm)
ΔG^0	Gibbs free energy
ΔH^0	enthalpy change
ΔS^0	entropy change
ε	molar absorptivity ($\text{mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$)
Eqn.	equation
<i>et al.</i>	et alia
GC-MS	Gas chromatography- mass spectrometry
Hz	Hertz
I	ionic strength (mol dm^{-3})
I_F	fluorescence intensity
ITC	isothermal titration calorimetry
J	coupling constant (Hz)
K	stability constant ($\text{dm}^3 \text{ mol}^{-1}$)
K_d	dimerisation constant ($\text{dm}^3 \text{ mol}^{-1}$) e.g. $2 \text{ RB} \rightleftharpoons (\text{RB})_2$
K_{11}	stability constant for 1:1 (host:guest) complexes ($\text{dm}^3 \text{ mol}^{-1}$), e.g. $\beta\text{-CD} + \text{Dye} \rightleftharpoons \beta\text{-CD}.\text{Dye}$
K_{12}	stepwise stability constant for 1:2 (host:guest) complexes ($\text{dm}^3 \text{ mol}^{-1}$) e.g. $\beta\text{-CD}.\text{Dye} + \text{Dye} \rightleftharpoons \beta\text{-CD}.\text{Dye}_2$
K_{21}	stepwise stability constant for 2:1 (host:guest) complexes ($\text{dm}^3 \text{ mol}^{-1}$) e.g. $\beta\text{-CD}.\text{Dye} + \beta\text{-CD} \rightleftharpoons \beta\text{-CD}_2.\text{Dye}$
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
pH	$-\log[H^+]$
p <i>K</i>	$-\log[K]$
ppm	parts per million
<i>R</i> _f	retention factor (in TLC)
<i>R</i> _c	relative retention factor to native cyclodextrins (in TLC)
ROESY	rotating frame Overhauser spectroscopy
T	temperature (K)
TLC	thin-layer chromatography
UV/Vis	ultraviolet/visible
wt	weight

2. Chemicals

α -, β -, γ -CD	α -, β -, γ -cyclodextrin
6 β -CDTs	6 ^A - <i>O</i> -(4-methylbenzenesulfonyl)- β -cyclodextrin
6 β -CDNH ₂	6 ^A -amino-6 ^A -deoxy- β -cyclodextrin
6 β -CDN ₃	6 ^A -azido-6 ^A -deoxy- β -cyclodextrin
6 β -CDen	6 ^A -(2-aminoethyl)amino-6 ^A -deoxy- β -cyclodextrin
β -CD ₂ x	covalent linked β -cyclodextrin dimer, where x is a linker
66 β -CD ₂ su	<i>N,N'</i> -bis-(6 ^A -deoxy-6 ^A - β -cyclodextrinyl)-succinamide
66 β -CD ₂ ur	<i>N,N'</i> -bis-(6 ^A -deoxy-6 ^A - β -cyclodextrinyl)-urea
β -CD ₃ x	covalent linked β -cyclodextrin trimer, where x is a linker
β -CD ₃ bz	1,3,5- <i>N,N,N</i> -tris(6 ^A -deoxy-6 ^A - β -cyclodextrin)-benzene
β -CDen ₃ bz	1,3,5- <i>N,N,N</i> -tris(6 ^A -(2-aminoethyl)amino-6 ^A -deoxy-6 ^A - β -cyclodextrin)-benzene
en	1,2-diamino ethane
hn	1,6-diamino hexane

ddn	1,12-diamino dodecane
C12	dodecyl
C18	octadecyl
AD	adamantane
DS	Dansyl
CV ⁺	Crystal Violet
PB ⁺	Pyronine B
RB	Rhodamine B
ADNH ₂	1-amino-adamantane
ADen	1-(2-aminoethyl)amino-adamantane
ADhn	1-(6-aminohexyl)amino- adamantane
ADddn	1-(6-aminododecyl)amino- adamantane
DSen	1-(2-aminoethyl)amino-dansyl
DShn	1-(6-aminohexyl)amino-dansyl
DSddn	1-(6-aminododecyl)amino-dansyl
PAA	poly(acrylic acids) or poly(acrylate)s
PAAC12	PAA with 3% substituents C12
PAAC18	PAA with 3% substituents C18
PAAAD	PAA with 3% substituents AD
PAAADen	PAA with 3% substituents ADen
PAAADhn	PAA with 3% substituents ADhn
PAAADddn	PAA with 3% substituents ADddn
PAADSen	PAA with 3% substituents DSen
PAADShn	PAA with 3% substituents DShn
PAADSddn	PAA with 3% substituents DSddn
NMP	<i>N</i> -methyl-2-pyrrolidinone
TFA	trifluoroacetic acid
THF	tetrahydrophuran