Applications of molecular modeling methods to Host-guest supramolecular chemistry

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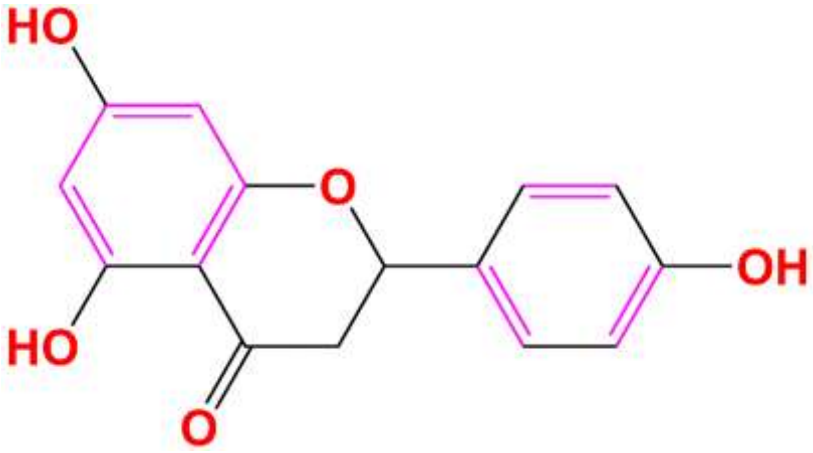
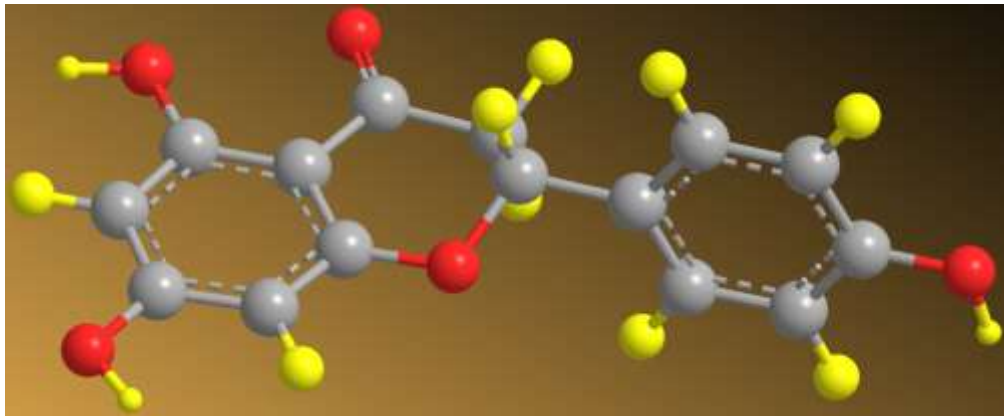
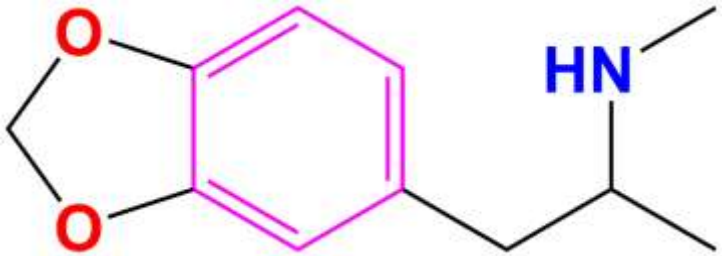
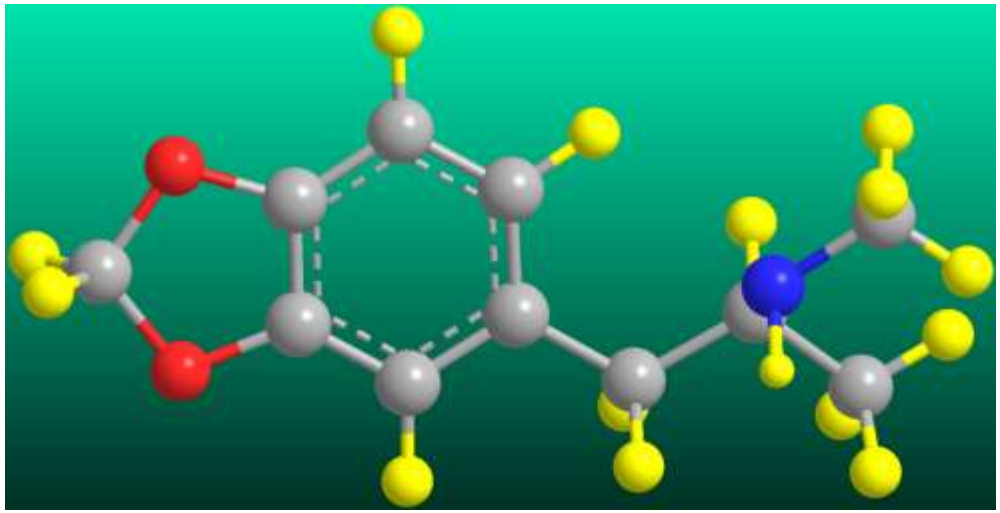
Molecular Chemistry

The chemistry of covalent bonding



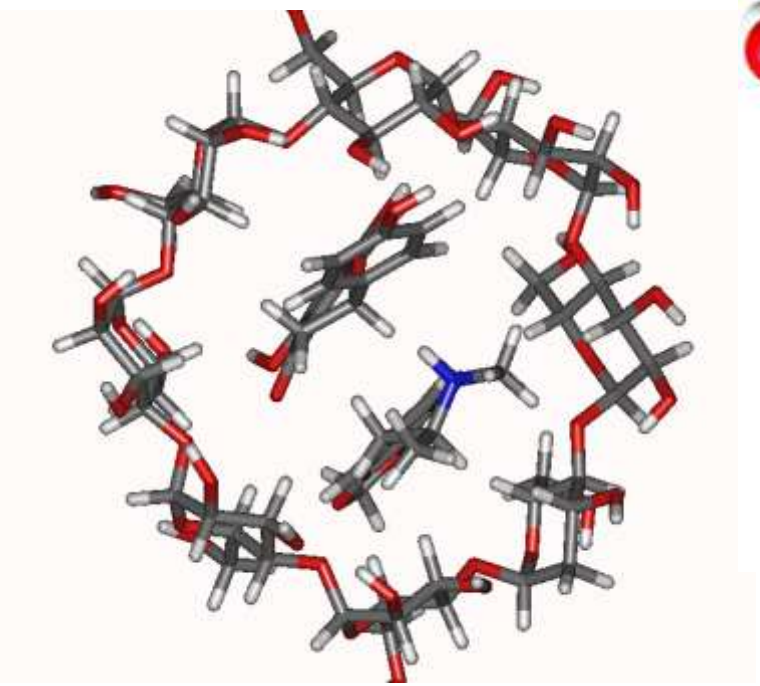


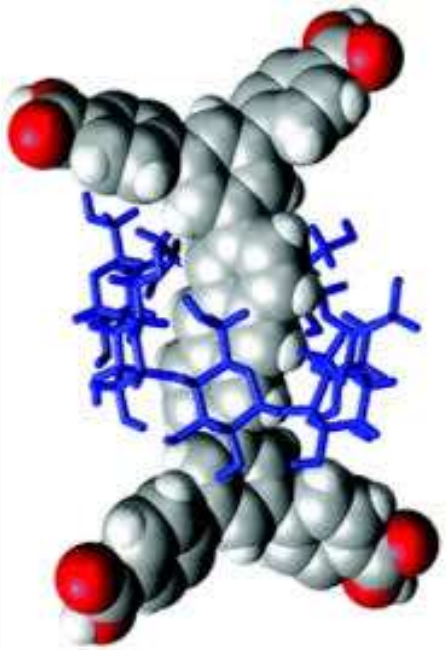


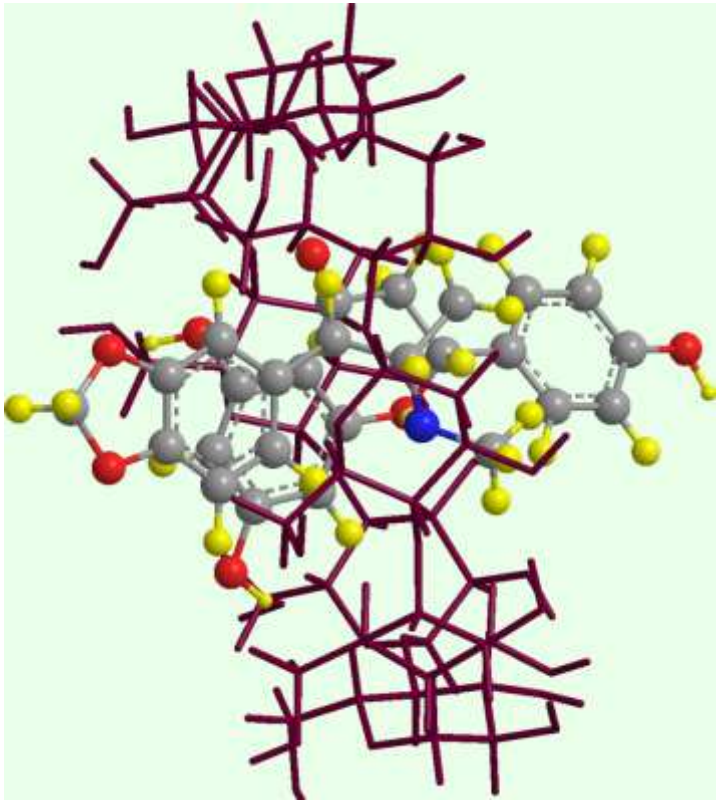


Supramolecular Chemistry

- **The chemistry beyond molecules based on intermolecular interactions**

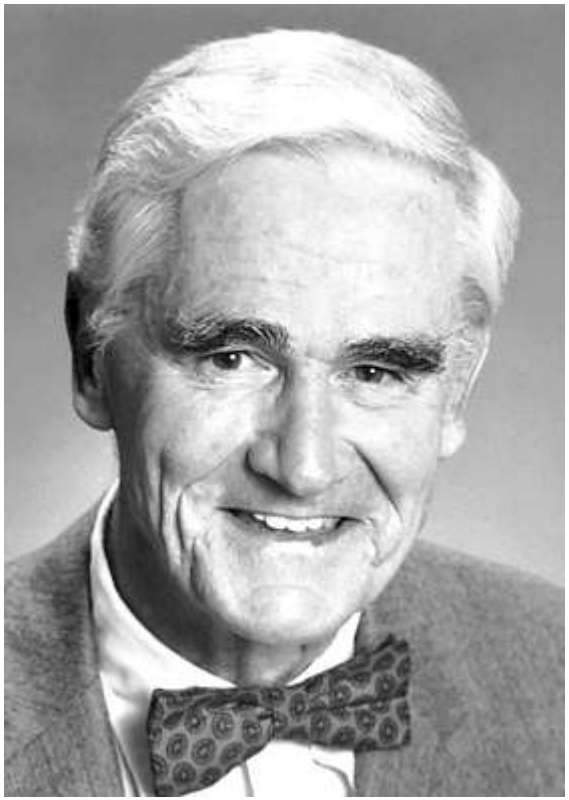






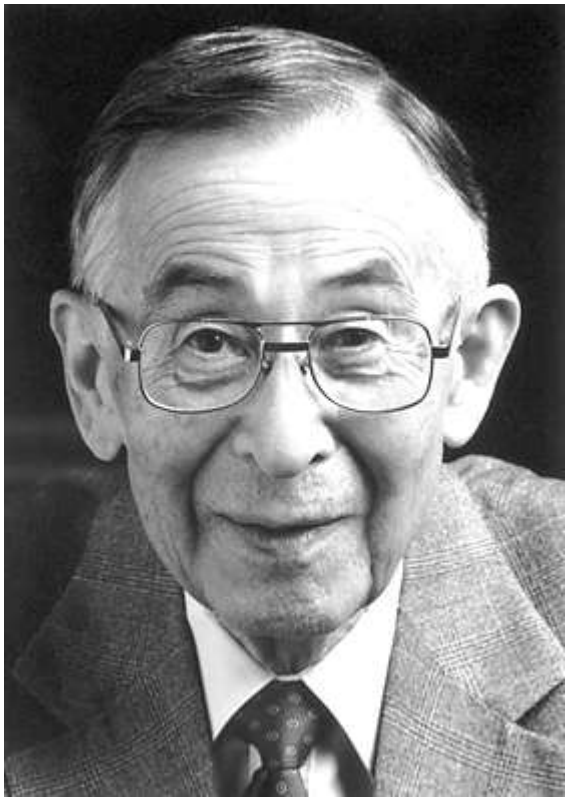
Supramolecular Chemistry

✹ Nobel Prize in Chemistry 1987



Donald J. Cram
University of California, Los Angeles

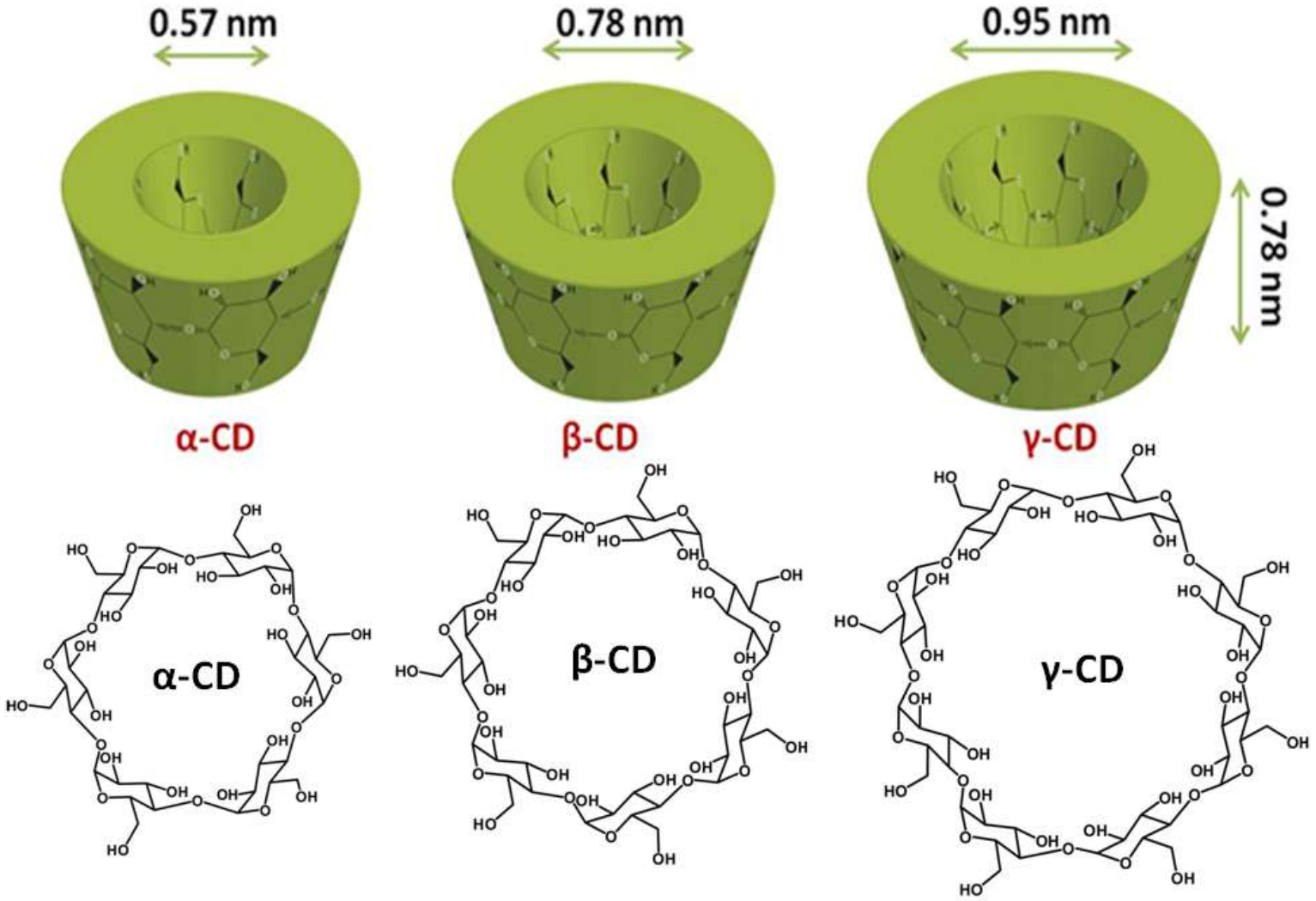
Jean-Marie Lehn
Université Louis Pasteur, Strasbourg, France,



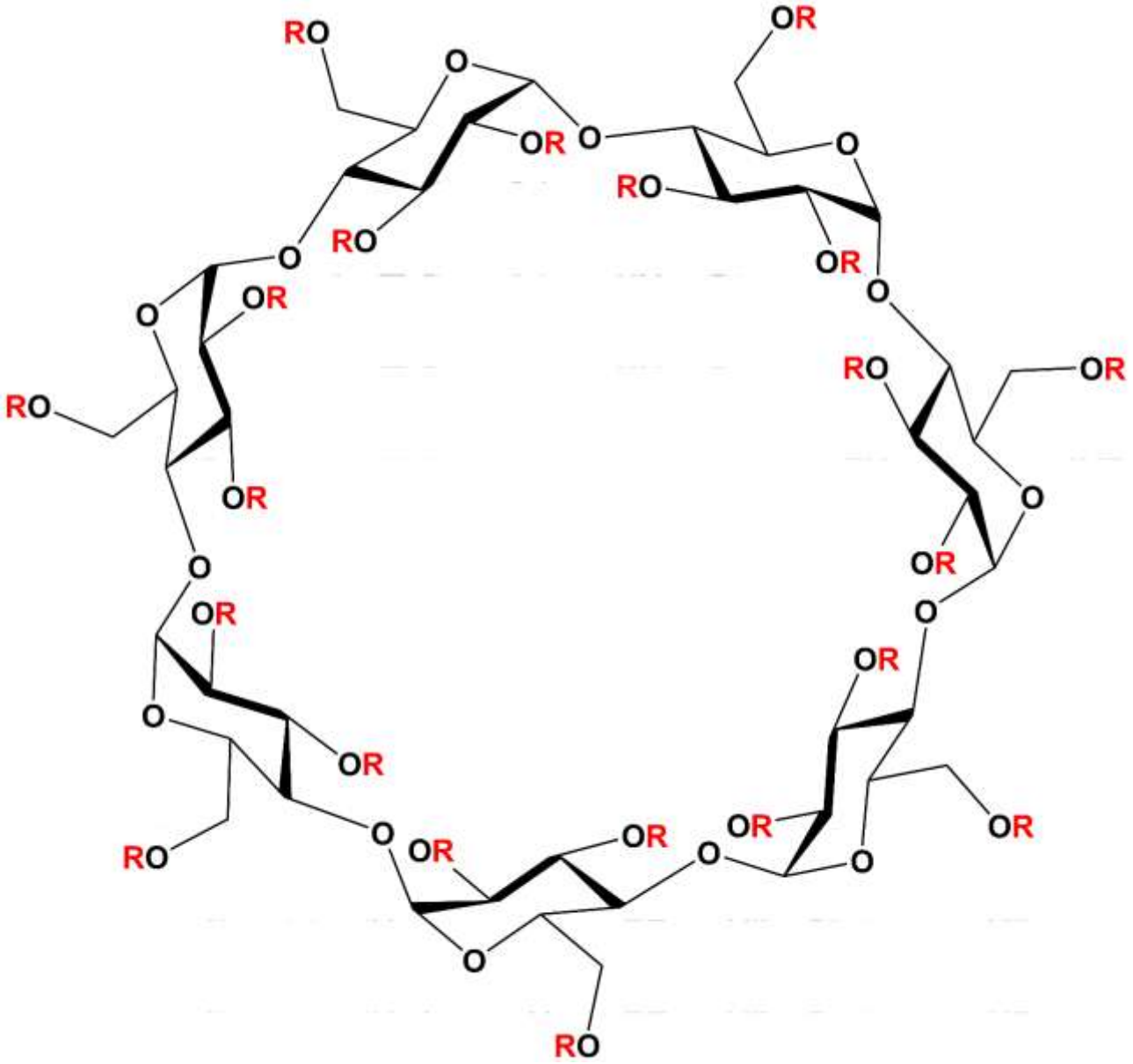
Charles J. Pedersen
Du Pont, Wilmington, USA

Cyclodextrins (CDs)

CDs are Cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose



Cyclodextrin Derivatives

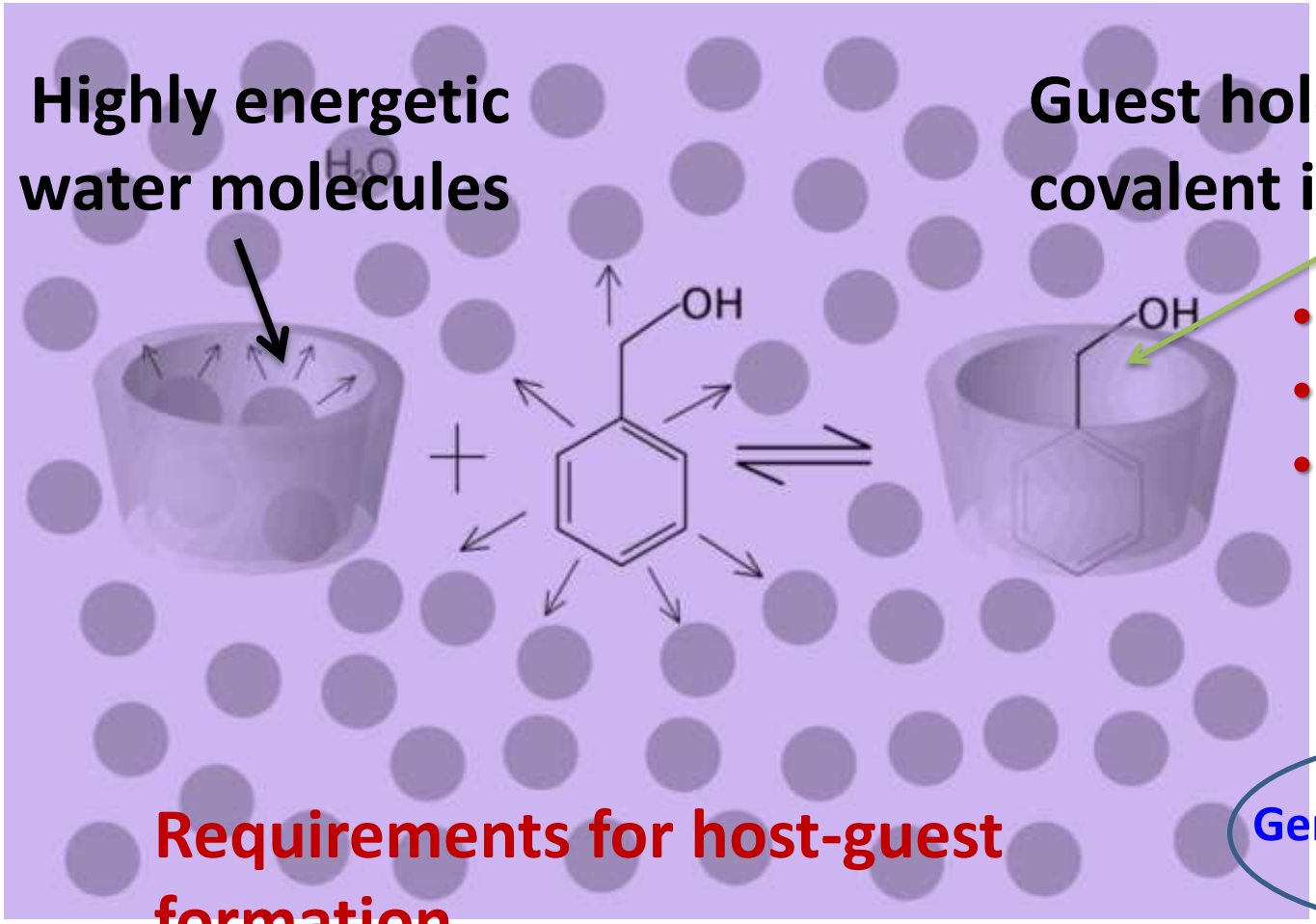


R = H / CH_3 Methyl-β-CD

R = H / $CH_3CH(OH)CH_2$- 2-hydroxypropyl-β-CD

R = H / $-CH_2CH_2-OH$ hydroxyethyl-β-CD

Inclusion complexes



- van der Waals
- H-bonding
- Dipole-dipole interaction

Generally weak!

Requirements for host-guest formation

- Size of guest and host
- Charge and Polarity of guest

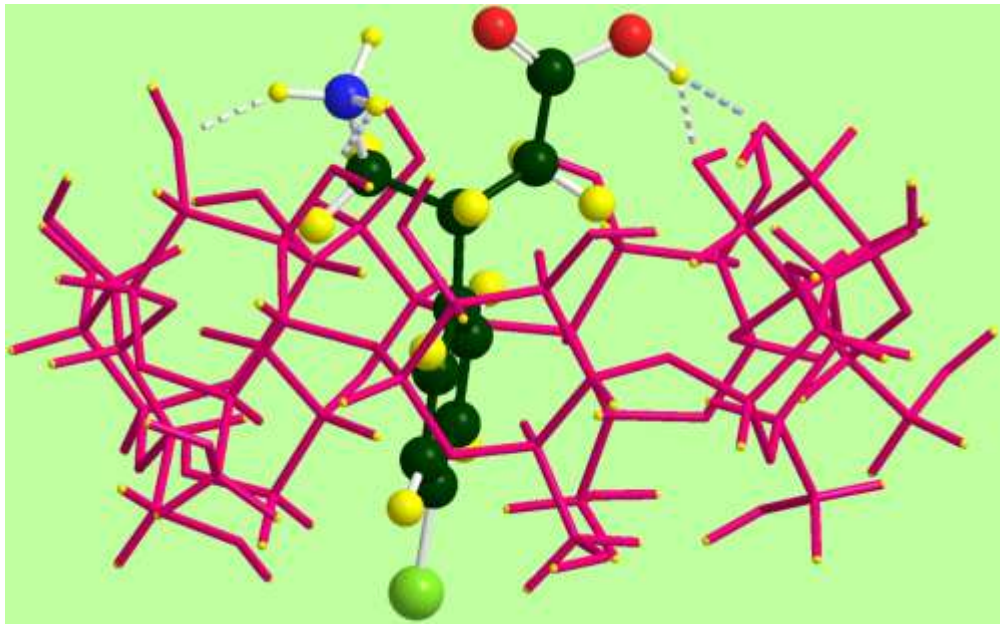
What drives the formation of the inclusion complex?

- **Reaction is spontaneous when Gibb's free energy $\Delta G<0$**

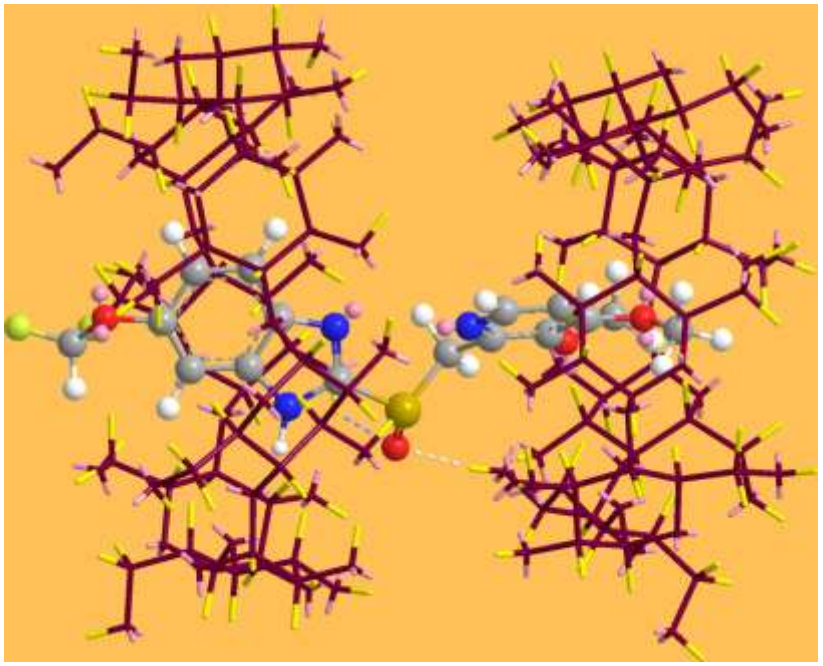
$$\Delta G = \Delta H - T\Delta S$$

- **lowering the enthalpy of the system.**
  - **The presence of intermolecular interactions.**
  - **Release of highly energetic water.**
- **Entropy increases when the water is displaced by the guest.**

Stoichiometry



1:1 guest : host complex



1:2 guest : host complex

Other stoichiometry are also possible e.g. 2:1 guest: host

Applications of CDs

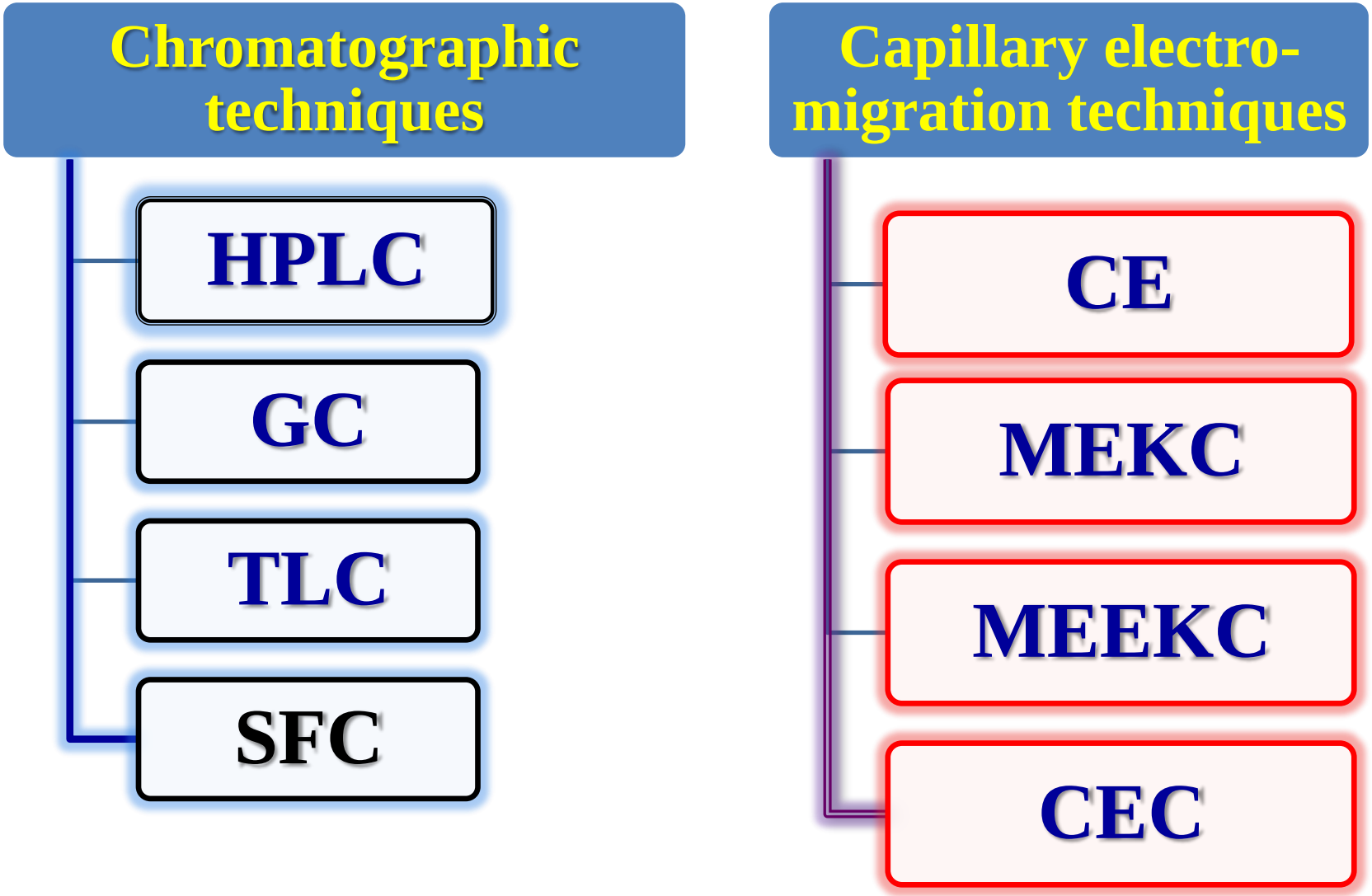
- **Pharmaceuticals**
  - Stability, solubility and bioavailability of drugs
- **Food**
  - Preparation of cholesterol-free products, authorized as dietary fibers, stabilize fragrance, remove unwanted taste and odor, etc.
- **Cosmetics.**
  - Stable active ingredients
  - Controlled release
- **Chromatography.**

Chiral molecules

- **Chiral molecules play an important role**
  - **Life sciences**
  - **Medical sciences**
  - **Synthetic chemistry**
  - **Food chemistry**

Analytical techniques capable of recognizing stereoisomers are important

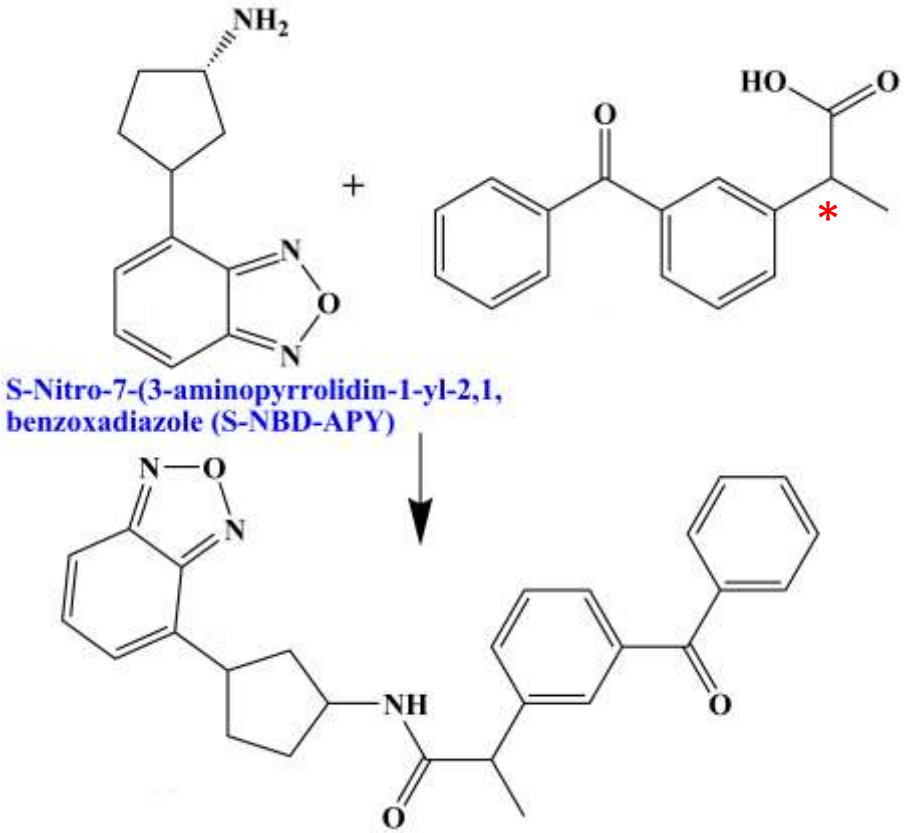
Enantioseparation techniques

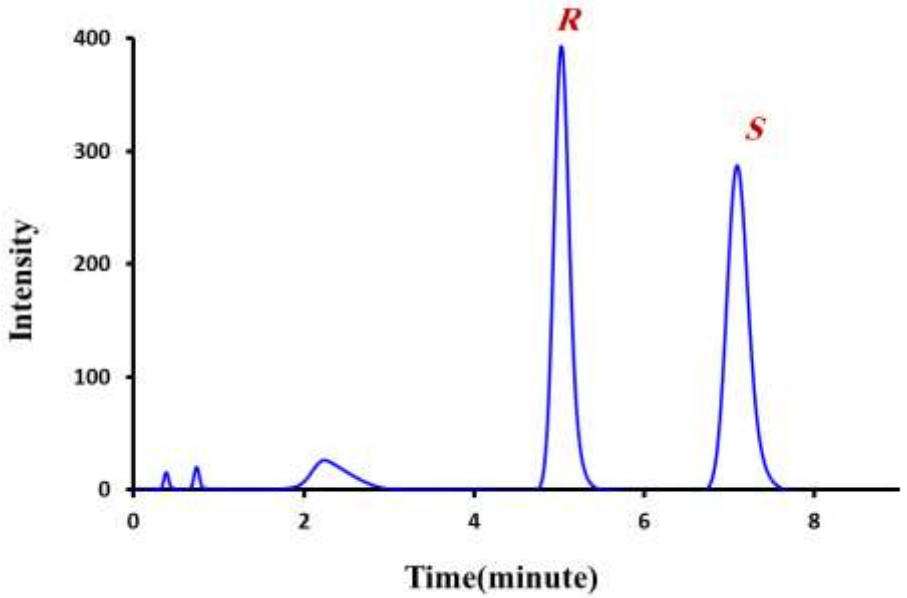


Methods of enantioseparations

Indirect method

- Enantiomers are derivatized with stereoisomeric pure reagent and the diastereomers formed are separated.





Methods of enantioseparations

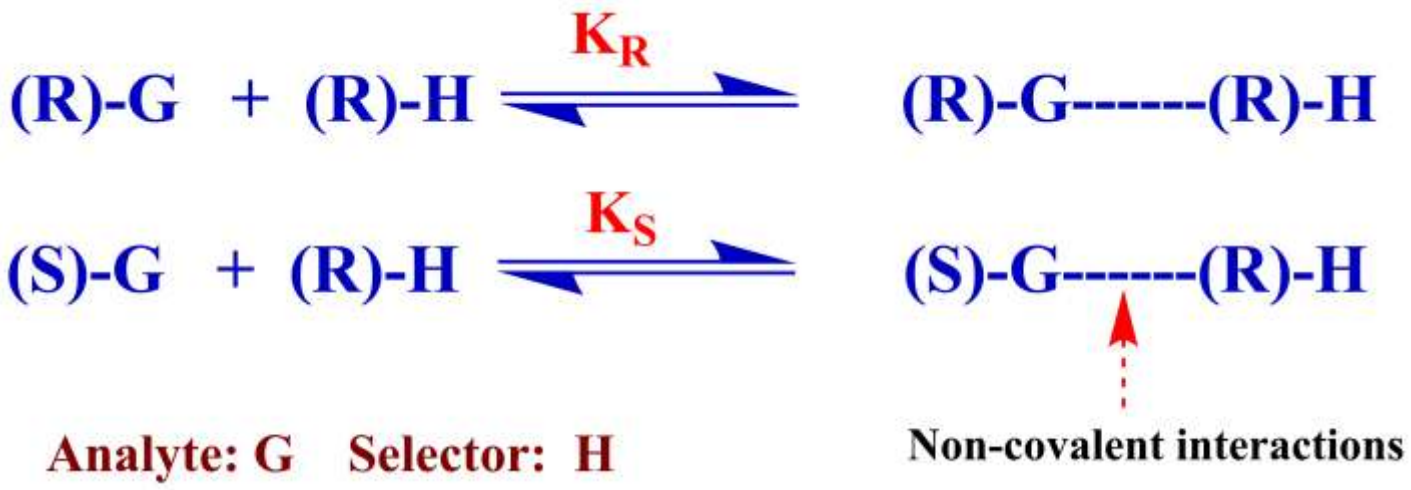
Direct method

- Involves separation of enantiomers due to the presence of a chiral selector
  - Fixed to stationary phase (HPLC, GC)
  - Added to mobile phase (HPLC) / background electrolyte (CE)

Enantioseparation is based on the formation of transient diastereomeric complexes (selector-analyte complex)

Model for indirect method

- **Based on the reversible formation of diastereomers between analyte and selector**

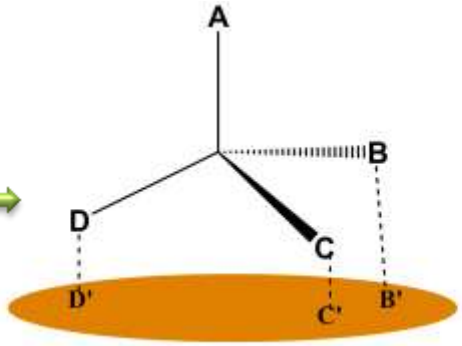


- **Differences between association constants K_R and K_S → basis for stereoselective recognition of enantiomers**

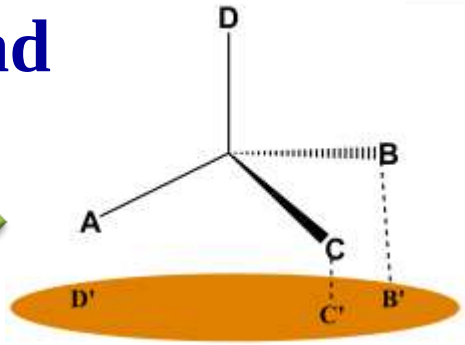
Three point attachment model

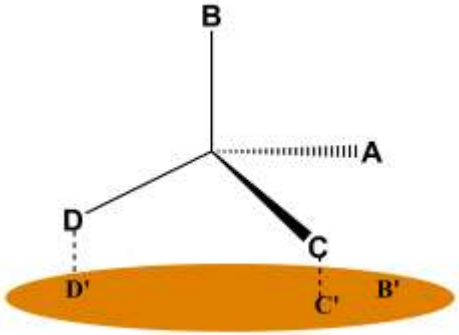
- One enantiomer form three interaction with selector (optimal fit)
- Other enantiomers form two interactions

Strongly bound (Ideal fit)



Less tightly bound (Non-ideal fit)



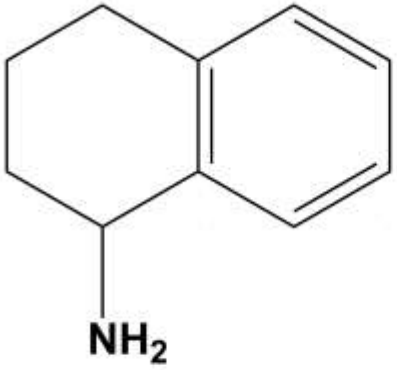


L.H. Easson, E. stedman**, Biochem. J**. 27 (1933) 1257.

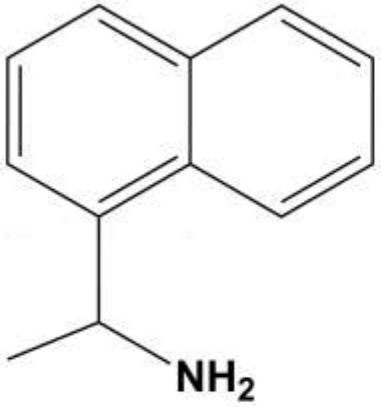
Techniques for chiral recognition mechanism

- **Spectroscopic techniques**
- **NMR**
  - **Nuclear Overhauser effect (NOE) – rotating frame Overhasuer effect (ROE)**
    - **Provide information on spatial proximity of atoms or substituents.**
- **X-ray crystallography for solid state complexes.**
- **Molecular modeling**
  - **Molecular mechanics, molecular dynamics, *ab-initio* methods, …**

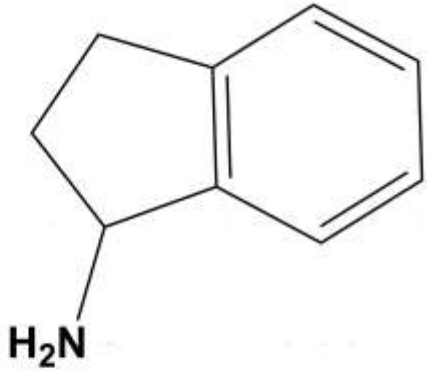
CE separation Dual System of 18-Crown-6 and β –Cyclodextrin*



1, 2, 3, 4-tetrahydro-1-naphthylamine (THAN)



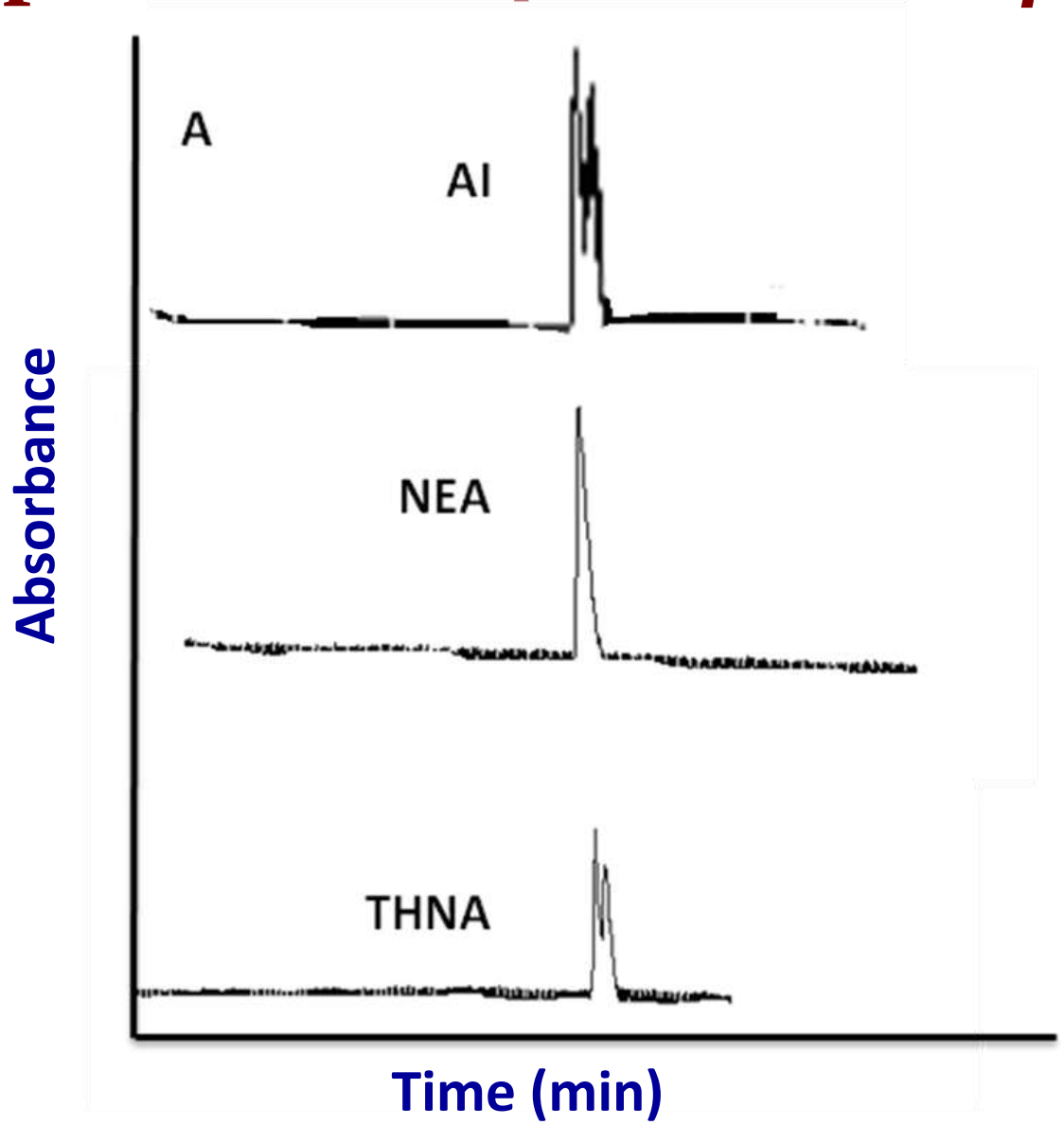
1-(1-naphthyl)Ethylamine (NEA)



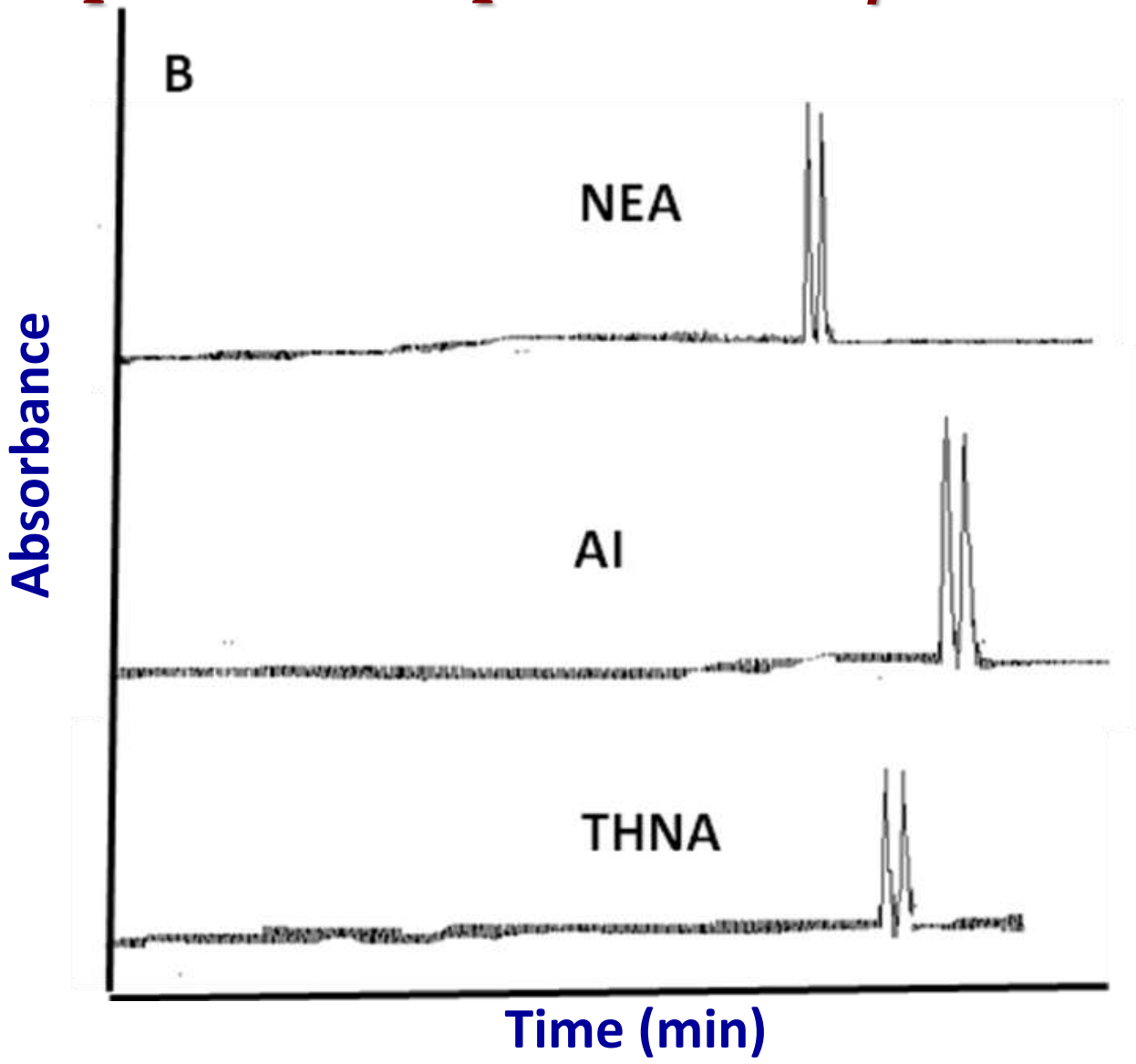
1-aminoindan (AI)

*A. A. Elbashir, F. O. Suliman, Journal of Chromatography A, 2011, 1218, 5344 - 5351

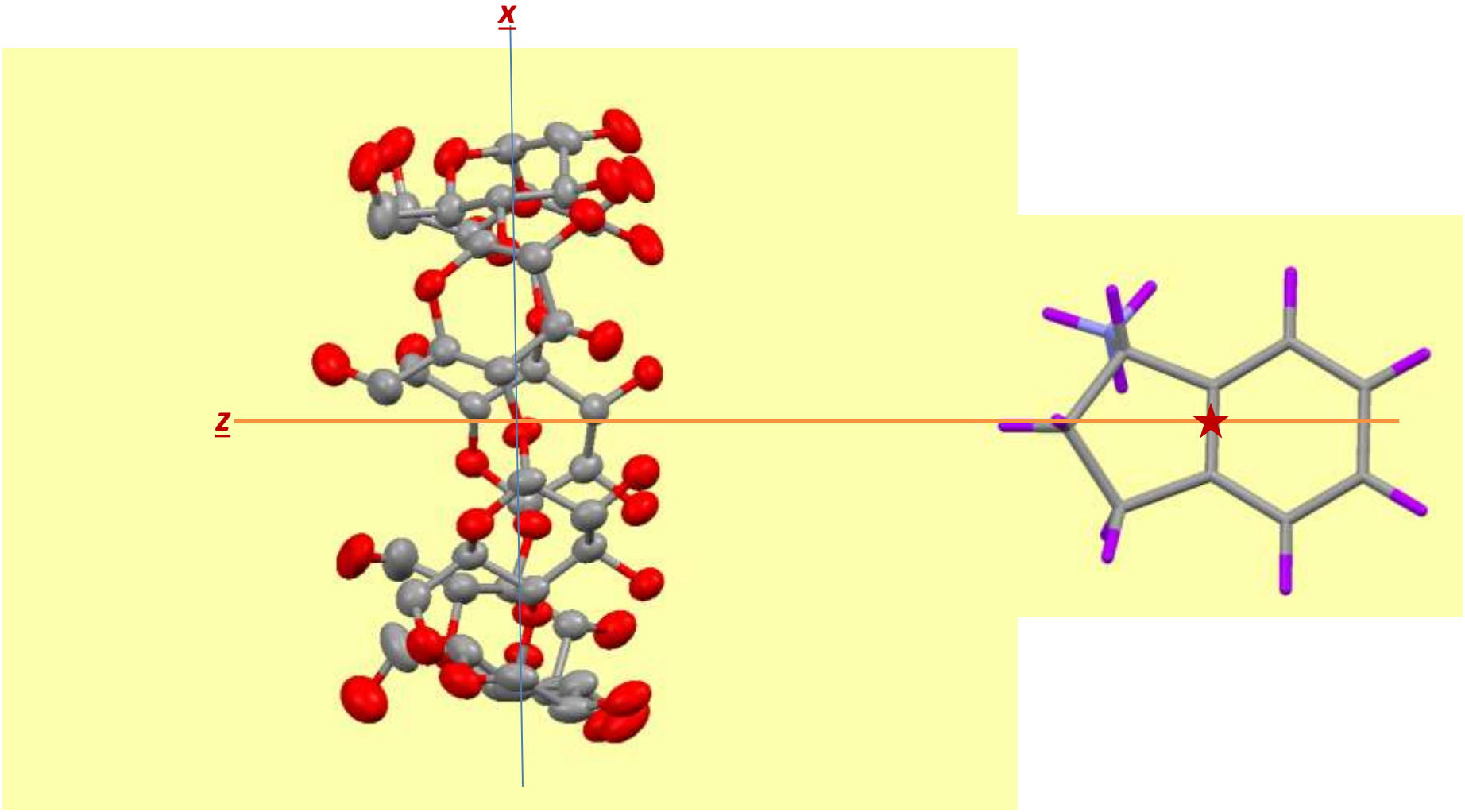
CE separation in presence of βCD



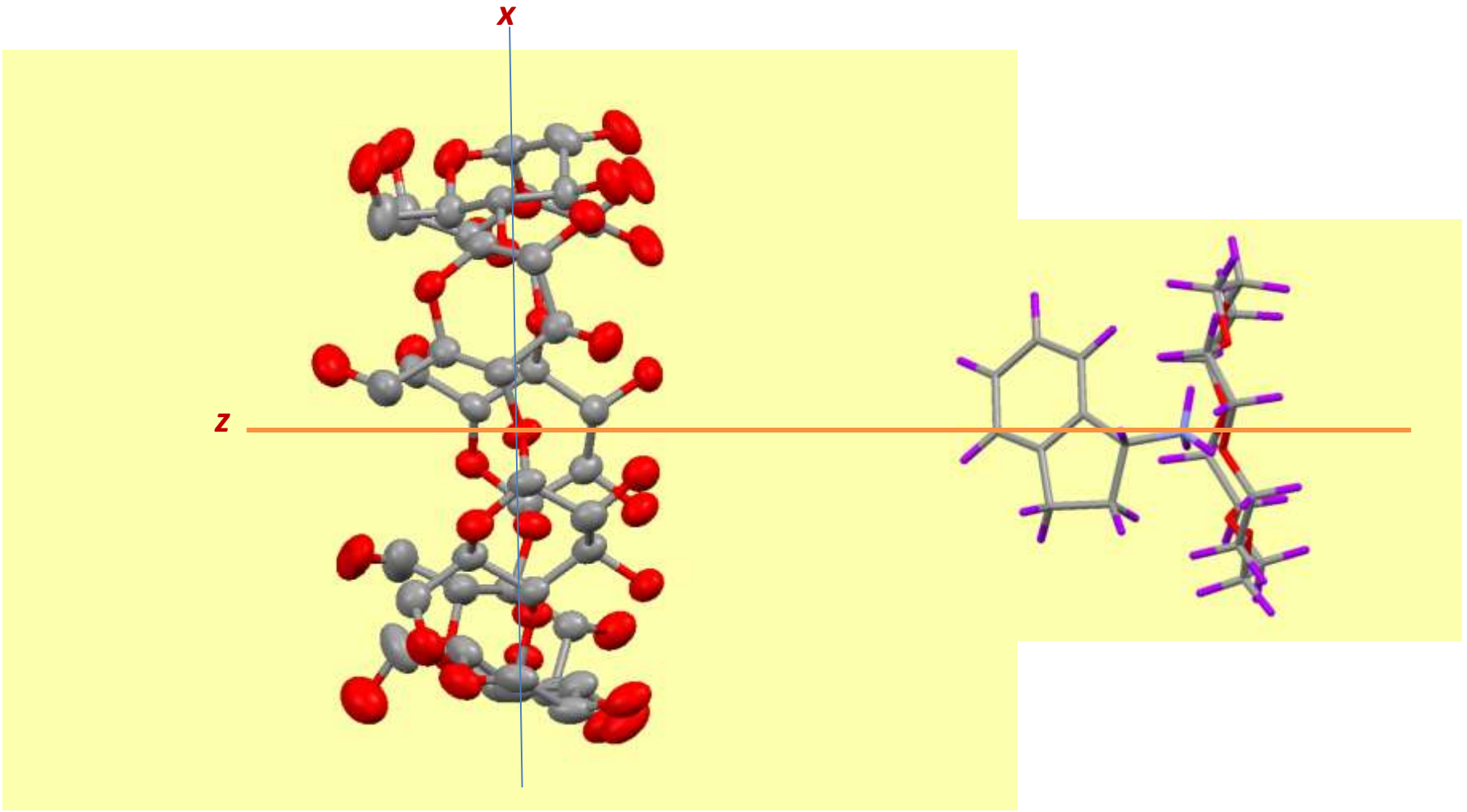
CE separation in presence of βCD and 18C6



Amine- βCD Complex formation



Sandwich Complex formation



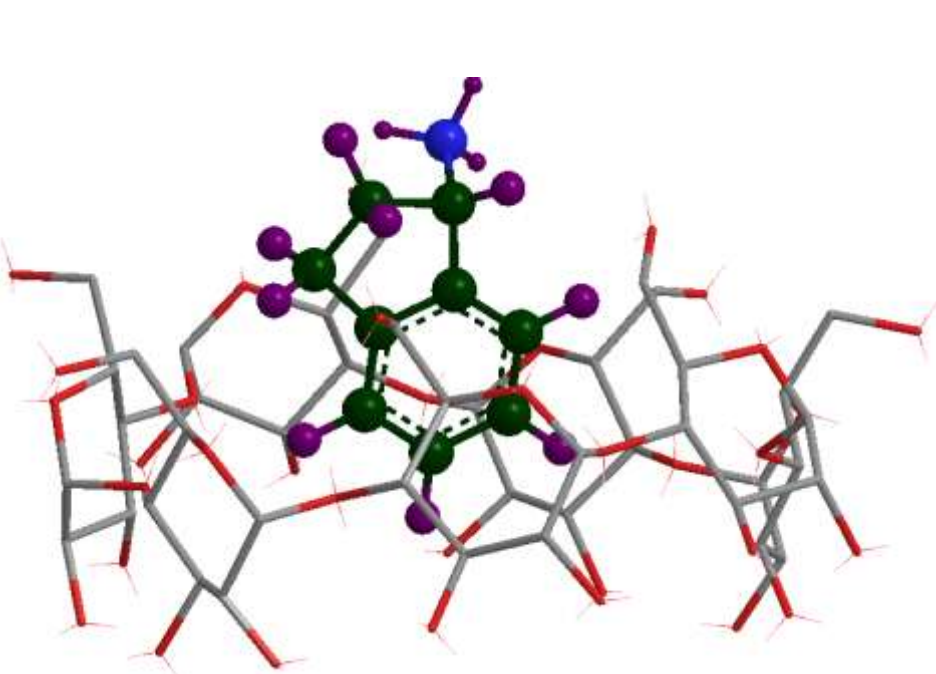
Interaction energies

	ΔE(Kcal mol^{-1})		ΔΔE(Kcal mol^{-1})
βCD -Complex	Orientation I	Orientation II	
R-AI	-50.3	-43.5	-4.7
S-AI	-55.0	-45.4	
R-NAE	-44.9	-42.7	-1.1
S-NEA	-46.0	-34.2	
R-THNA	-48.9	-46.7	-2.0
S-THNA	-50.1	-49.1	
R-AI-18C6	-64.9	-58.2	6.2
S-AI-18C6	-57.3	-58.7	
R-NEA-18C6	-54.2	-58.2	-5.7
S-NEA-18C6	-63.9	-60.2	
R-THNA-18C6	-59.1	-66.8	4.1
R-THNA-18C6	-62.7	-59.5	

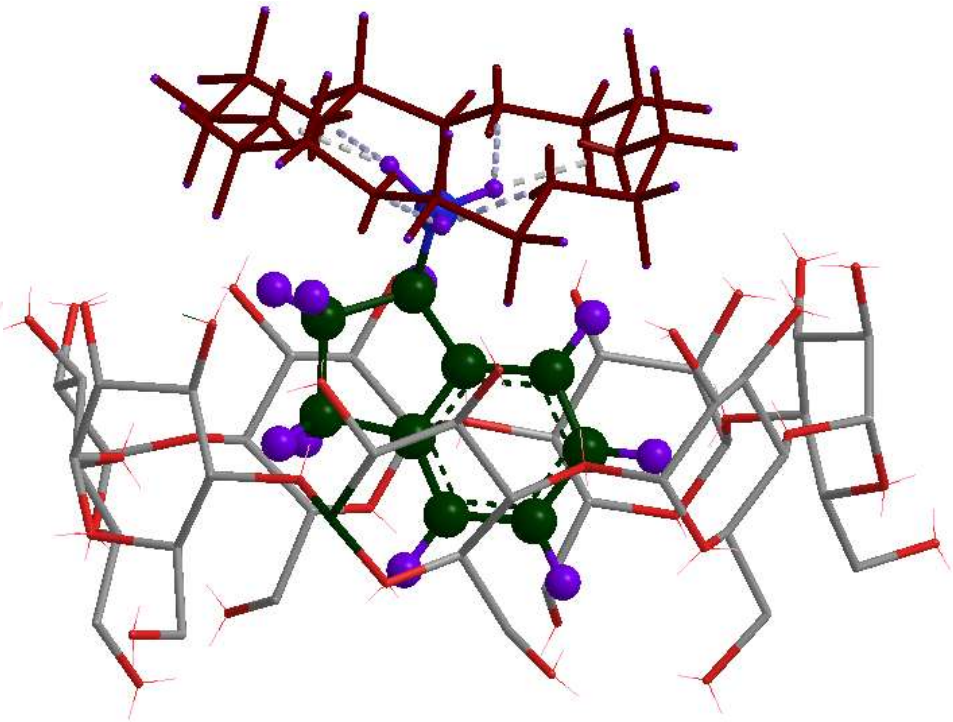
$\Delta\Delta E = \Delta E_S - \Delta E_R$

negative sign of ΔΔE indicates that the R-isomer is eluted first.

AI complexes

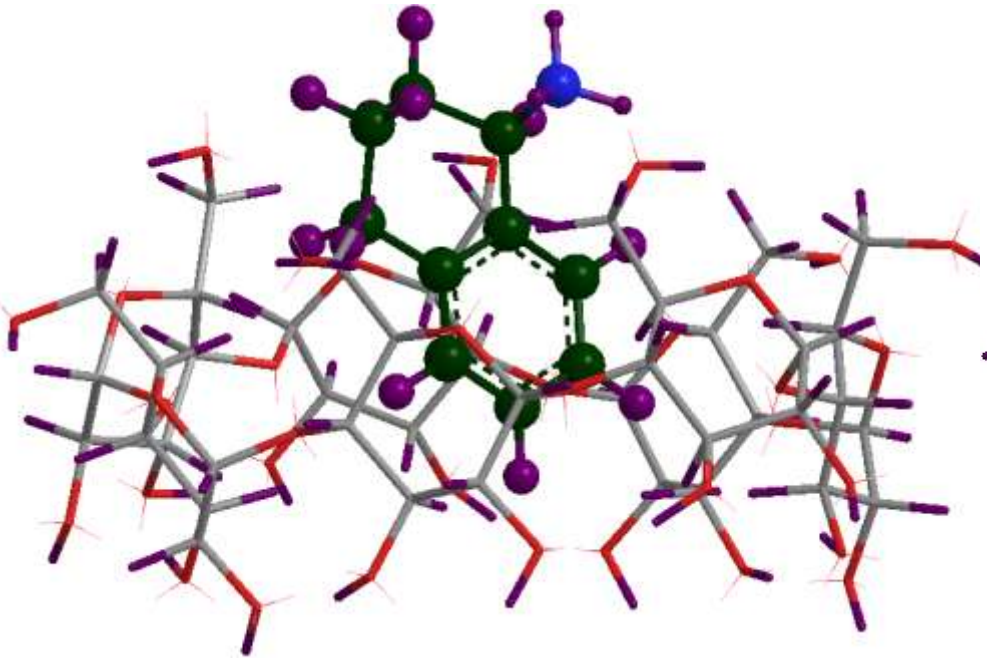


Binary complex

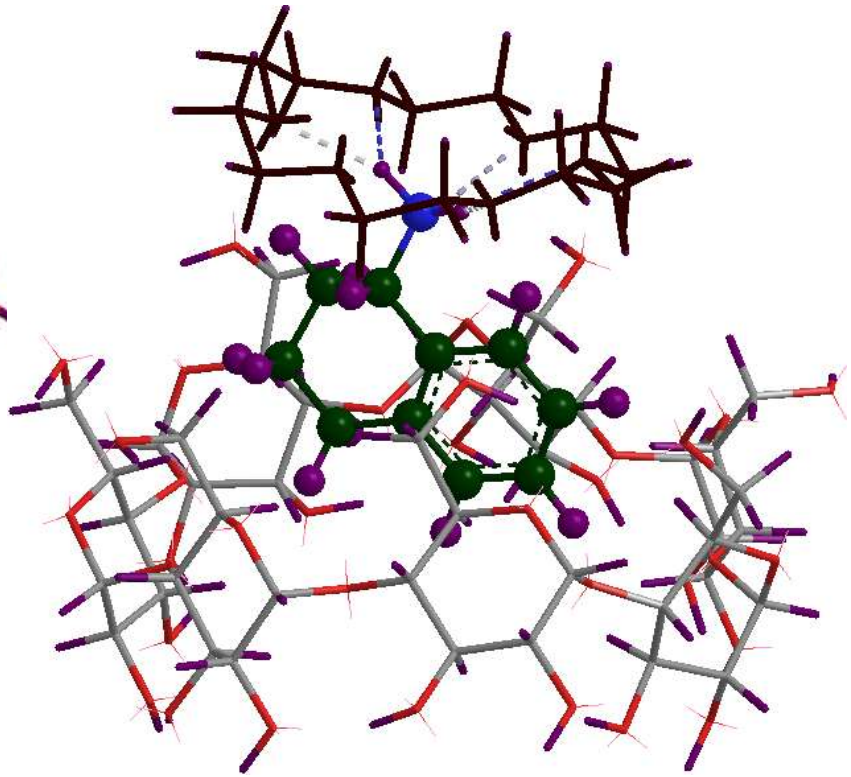


Ternary complex

THNA complexes



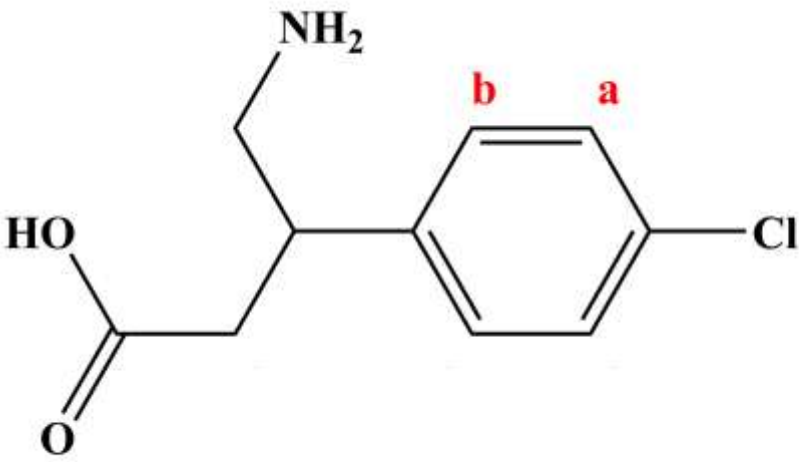
Binary complex



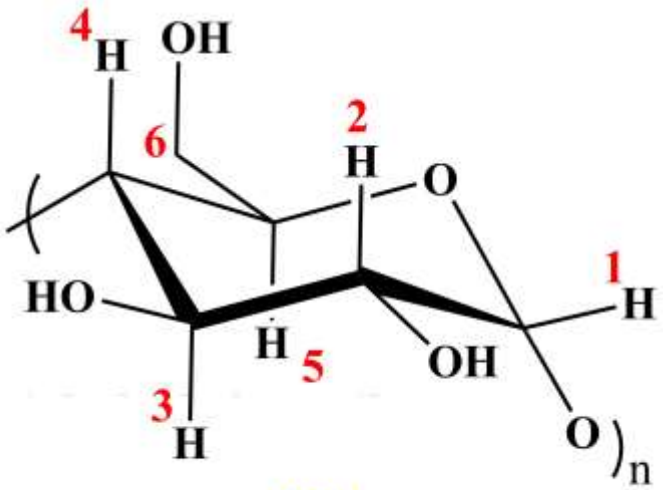
Ternary complex

CE separation of baclofen (BF)*

- **BF is a γ-aminobutyric acid analog and is extensively used as**
  - **Stereoselective agonist for $GABA_B$ receptor.**
  - **Muscle relaxant.**



BF

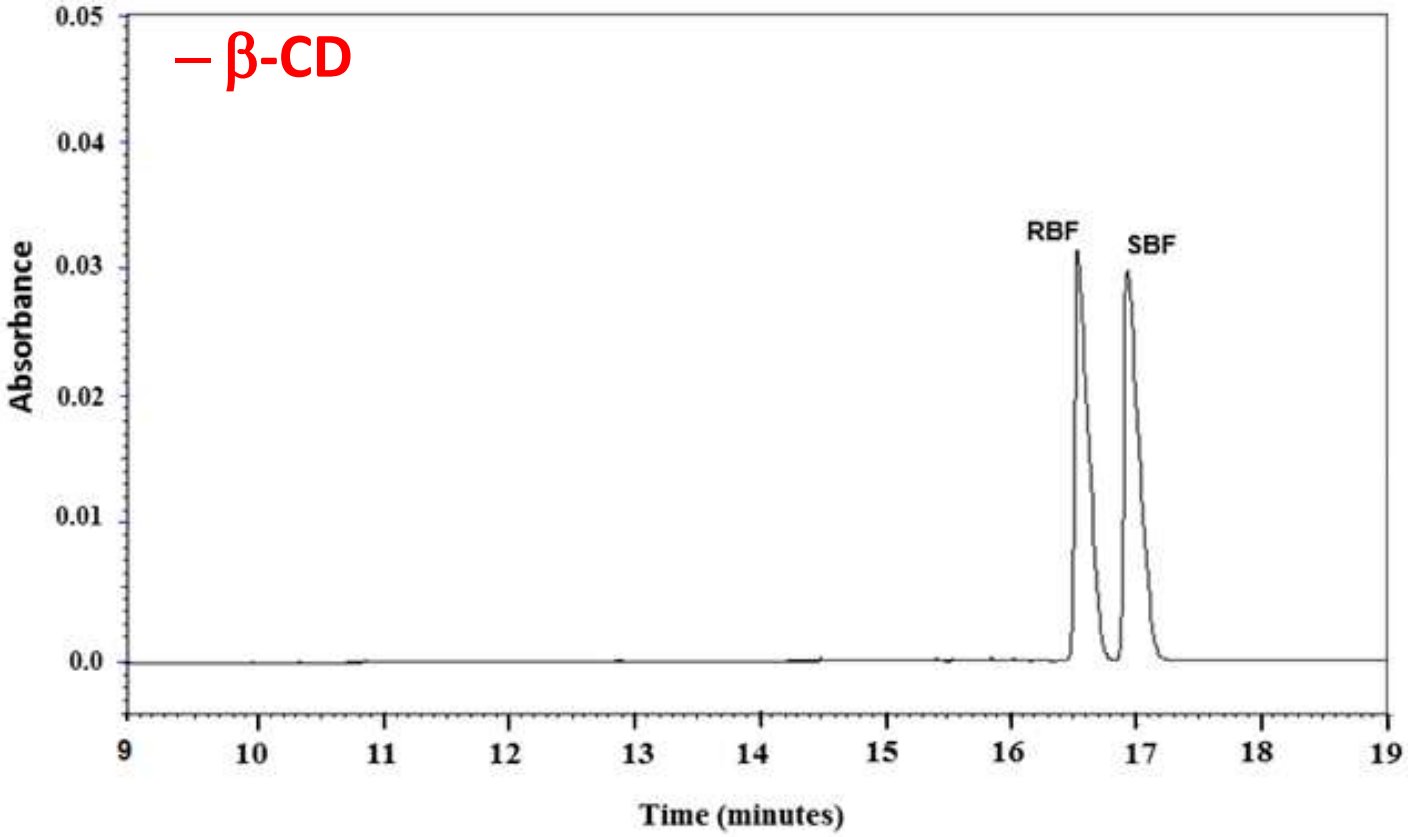


CD

*F. O. Suliman, A. A. Elbashir, *Journal of Molecular Structure*, 2012, 1019, 43-49

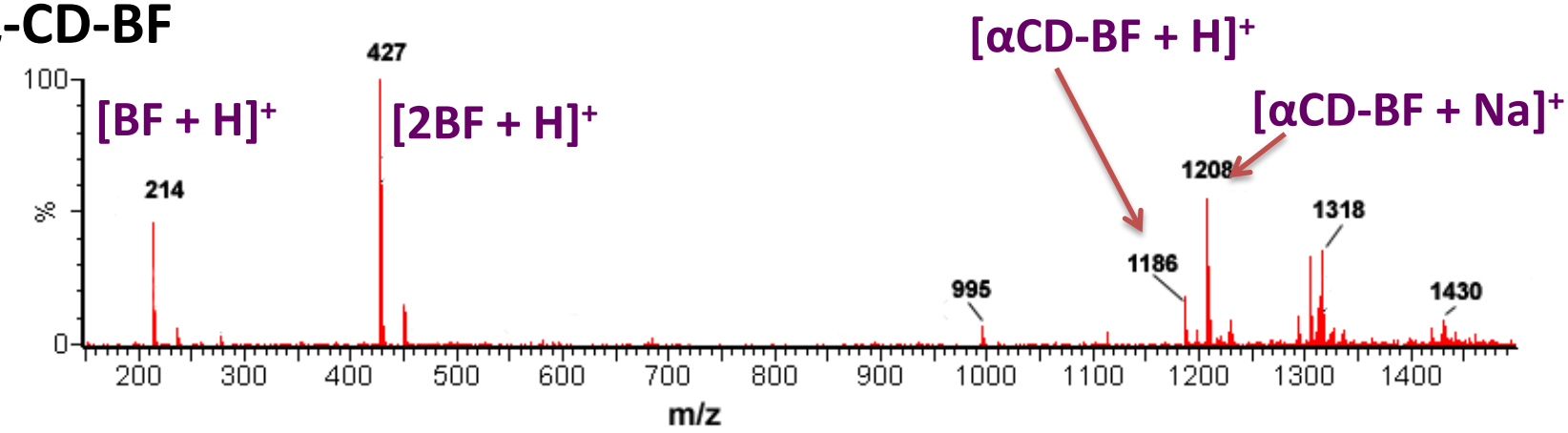
CE separation of BF

- **Chiral selectors: α-CD and β-CD**
  - **No separation in presence of α-CD**

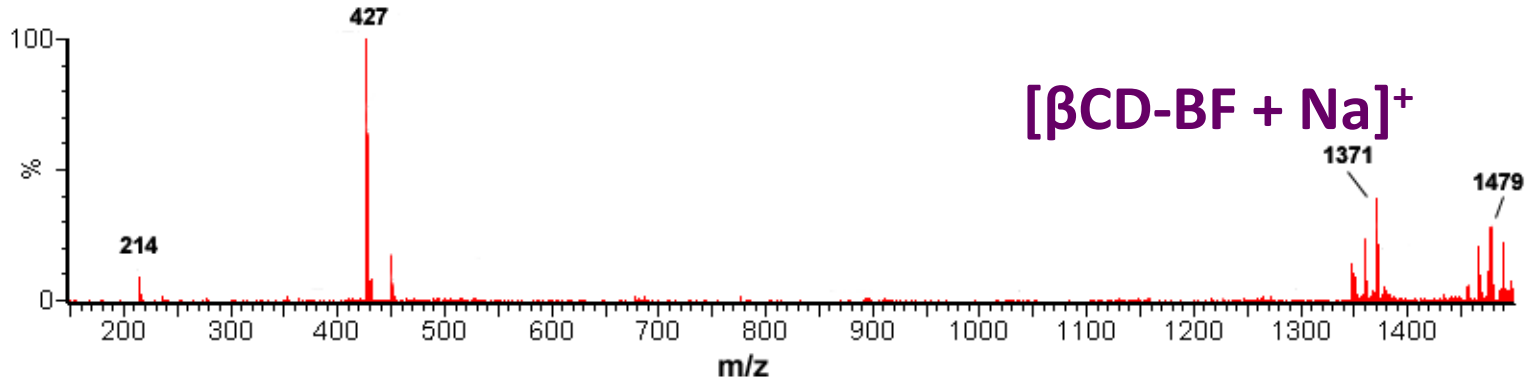


ESI-MS of BF-CD complexes

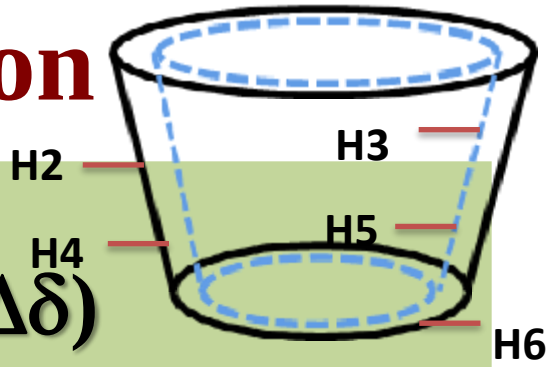
α-CD-BF



β-CD-BF



NMR: BF-βCD complexation



	Chemical Shift (Δδ)						
[BF]/[βCD]	H_2	H_3	H_4	H_5	H_6	H_a(BF)	H_b(BF)
0.16	-0.001	-0.008	-0.001	-0.008	0.000	0.083	0.034
0.64	-0.002	-0.032	-0.002	-0.016	-0.006	0.140	0.069
0.96	-0.004	-0.058	-0.008	-0.055	-0.004	0.177	0.091
1.60	-0.006	-0.061	-0.011	-0.053	-0.003	0.192	0.097

Molecular modeling

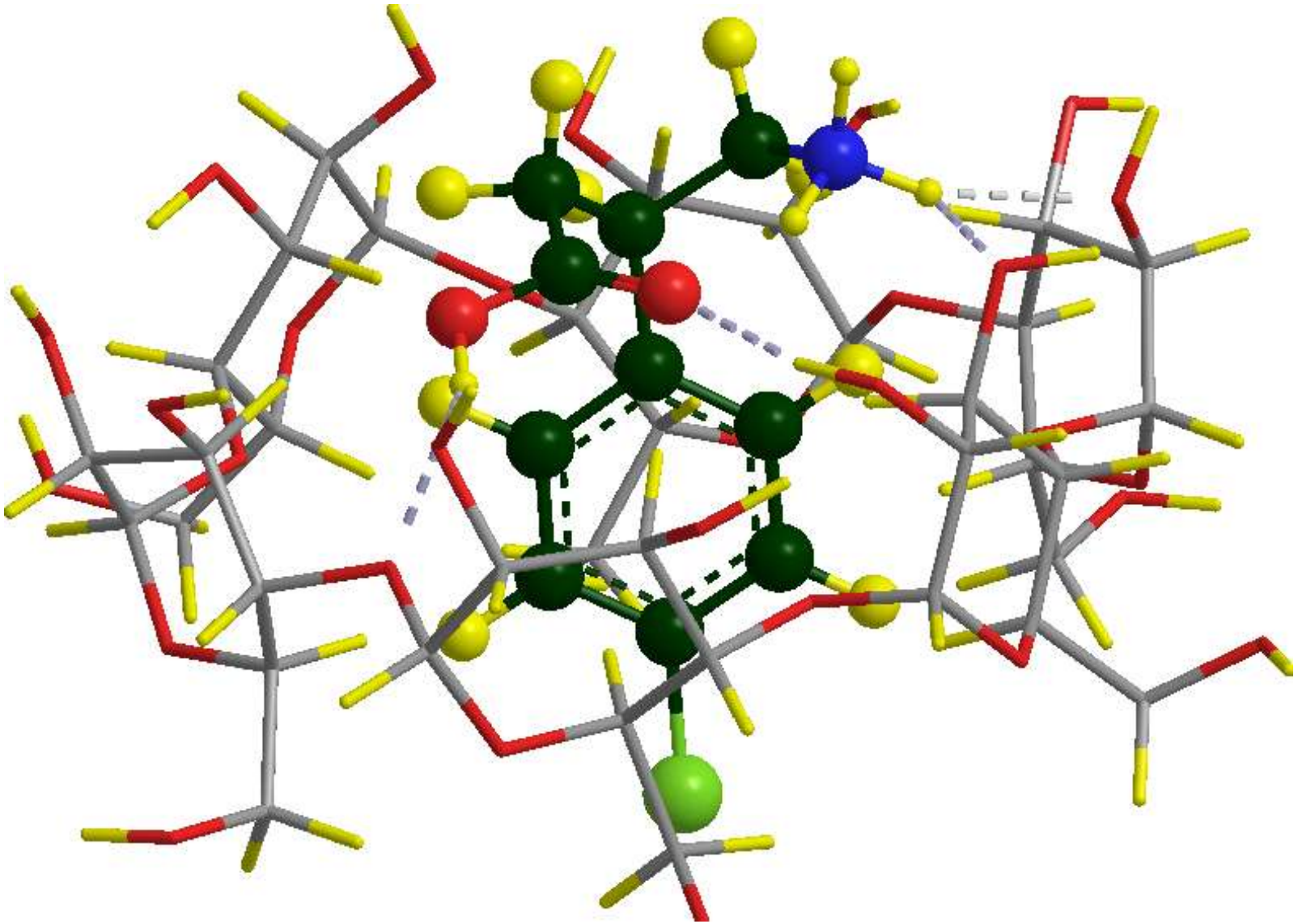
- **Docking of BF into CDs**
- **QM calculations on the inclusion complexes obtained by the docking procedures**
  - **PM6 method**

$$\Delta E = E_{comp} - (E_{BF} + E_{CD})$$

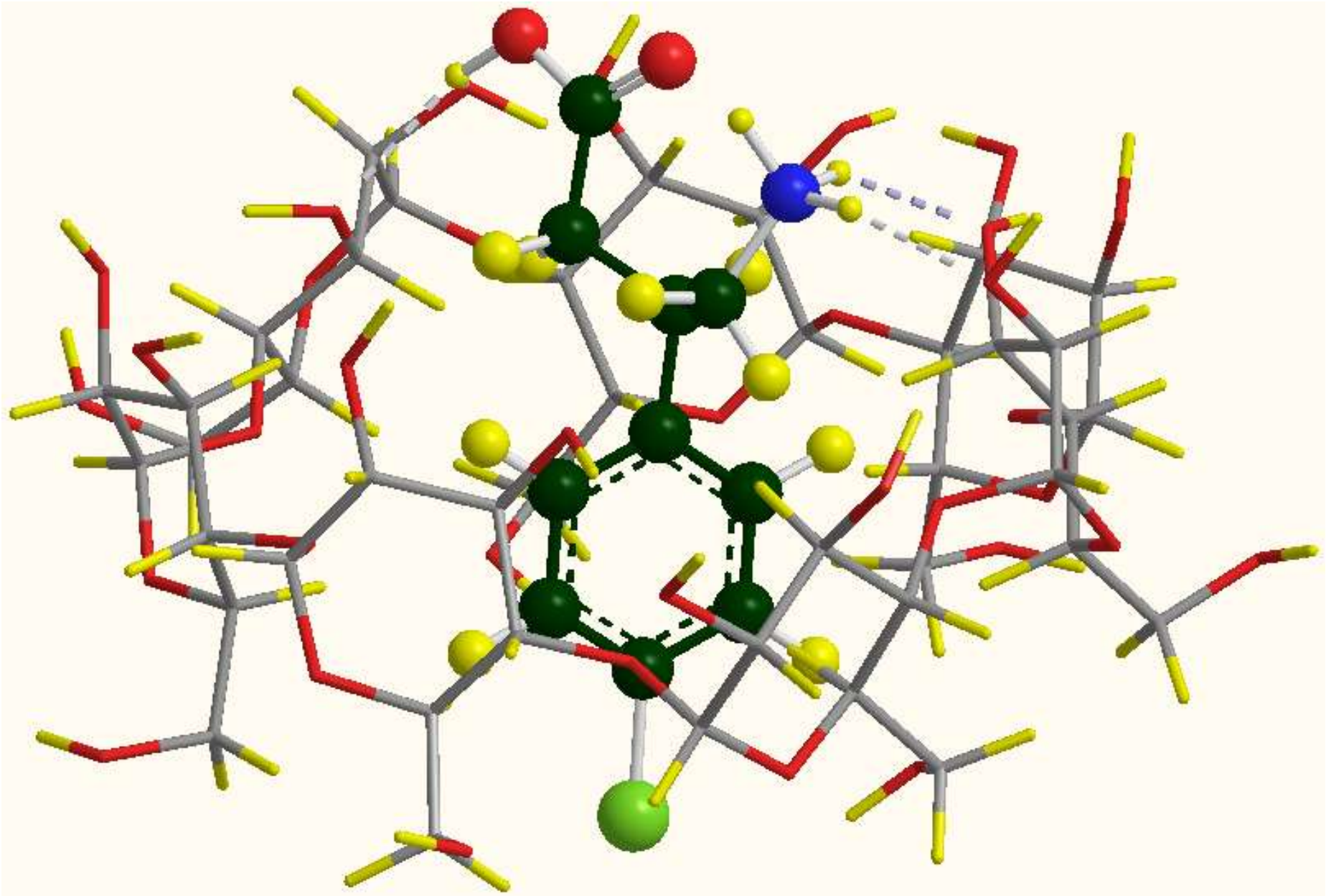
PM6 calculations

Parameter	R-BF/αCD	S-BF/αCD	R-BF/βCD	S-BF/βCD
E (kJ mol^{-1})	-5503.5	-5500.0	-6451.4	-6496.1
ΔE(kJ mol^{-1})	-128.3	-127.1	-131.8	-178.5
ΔΔE(kJ mol^{-1})	1.3		-46.8	
ΔH(kJ mol^{-1})	-132.3	-129.3	-131.2	-181.8
ΔS(J $mol^{-1}K^{-1}$)	-310.4	-285.2	-243.2	-295.5
ΔG(kJ mol^{-1})	-39.7	-44.3	-58.6	-93.8

Optimized R-BF-αCD



Optimized R-BF-βCD



Molecular dynamics simulations

- very powerful method in modern molecular modeling. Allows following structure and dynamics at scales where motion of individual atoms or molecules can be tracked
  - Statistical Mechanics!
- The trajectories of atoms and molecules are determined by solving the Newton's equation of motion for a system of interacting particles
- Limitations:
  - Lack of quantum effects
  - Limited time accessible (ns-μs)

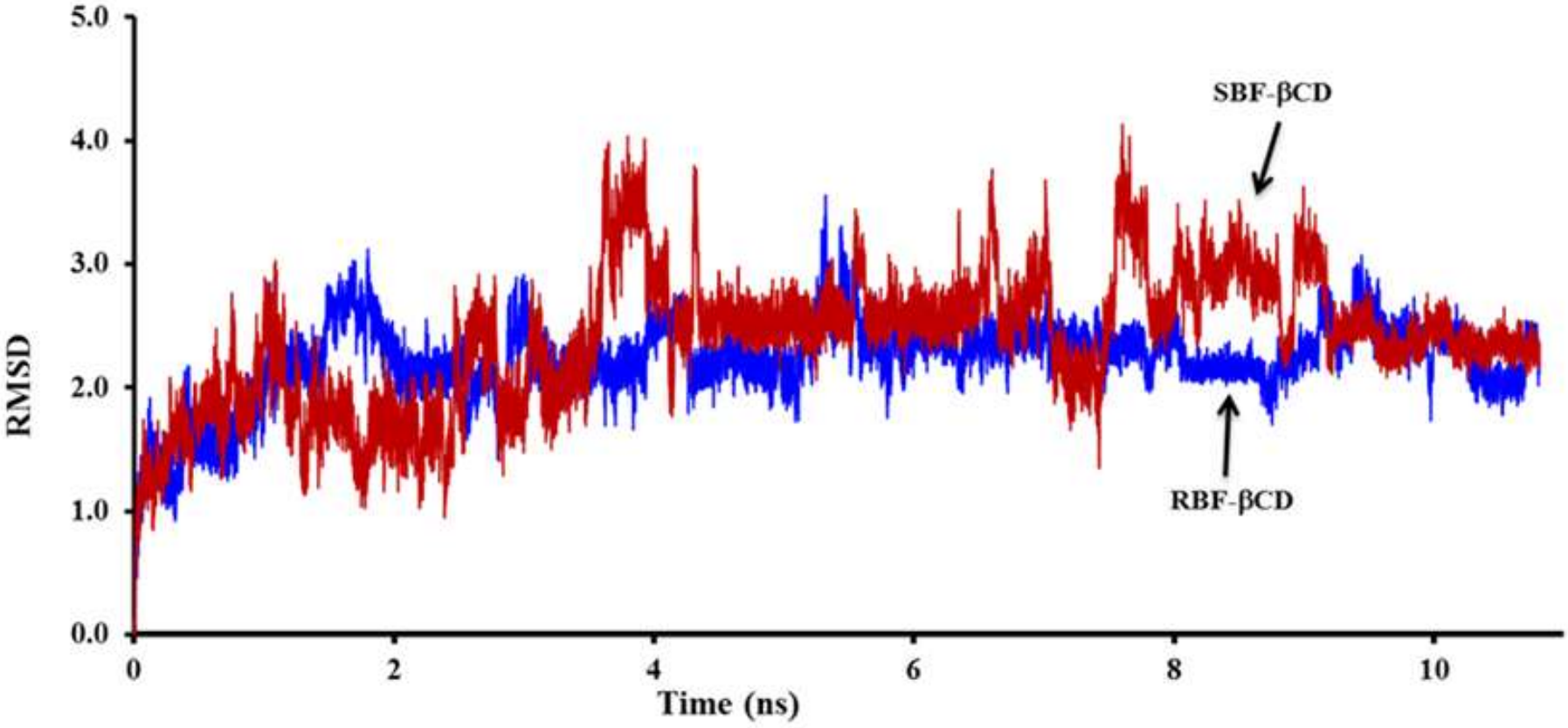
Software

- A number of free software
  - NAMD
  - https://en.wikipedia.org/wiki/List_of_software_for_molecular_mechanics_modeling
  - Some training is required!

Molecular dynamics simulations

- **Amber 11 software package (not totally free, but can be obtained at reduced price for academic use)**
  - **General force field parameter set.**
  - **Complexes solvated in truncated octahedral box of TIP3P water molecules.**
  - **Analysis of MD trajectories by ptraj.**
  - **H-bond analysis - hydrogen bond cut distance ≤3.0 Å and angle ≥120°**

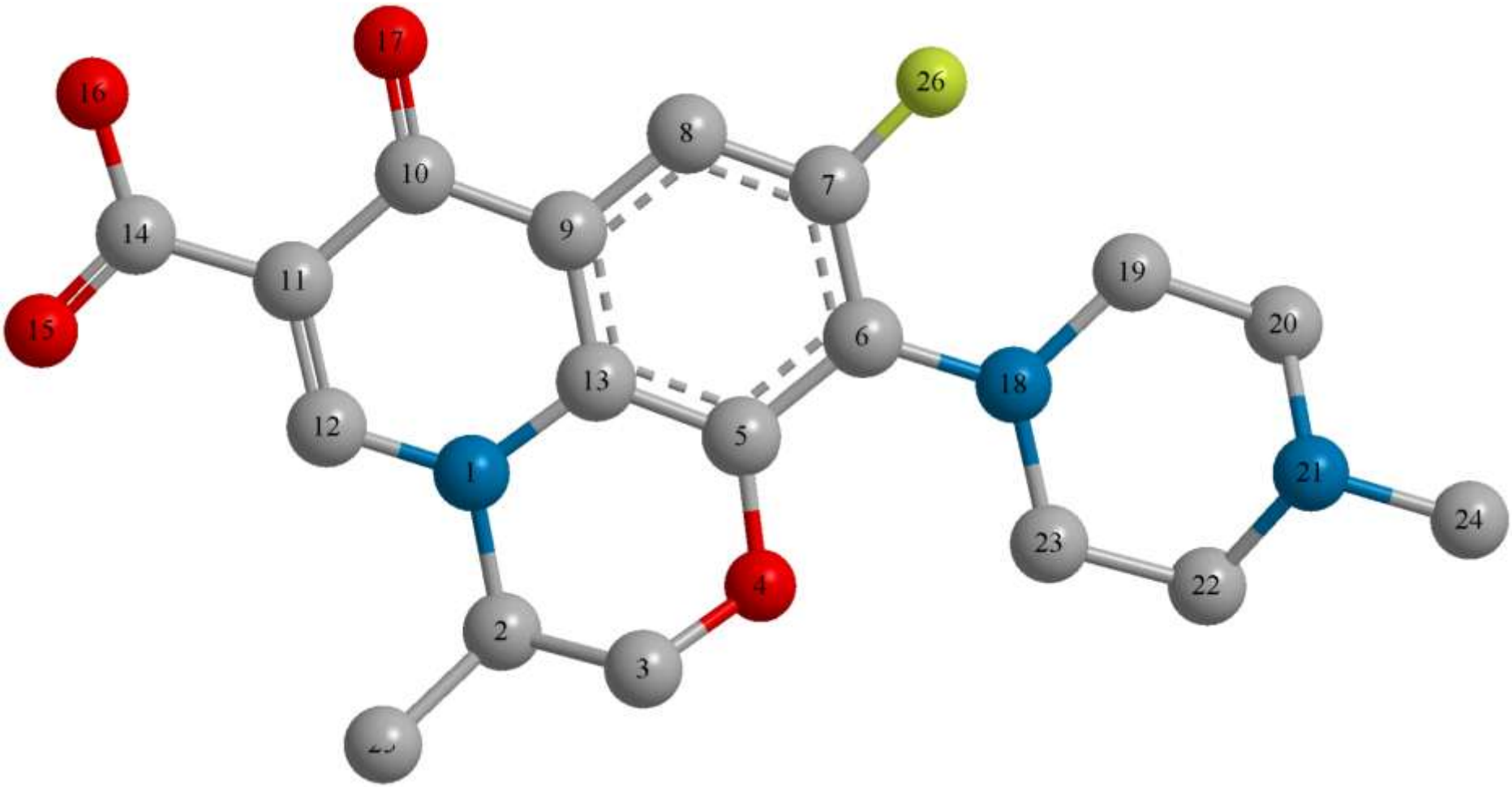
MD trajectories



Hydrogen bond occupancy and distance calculated during the last four nanosecond of the MD trajectories for S-BF-βCD

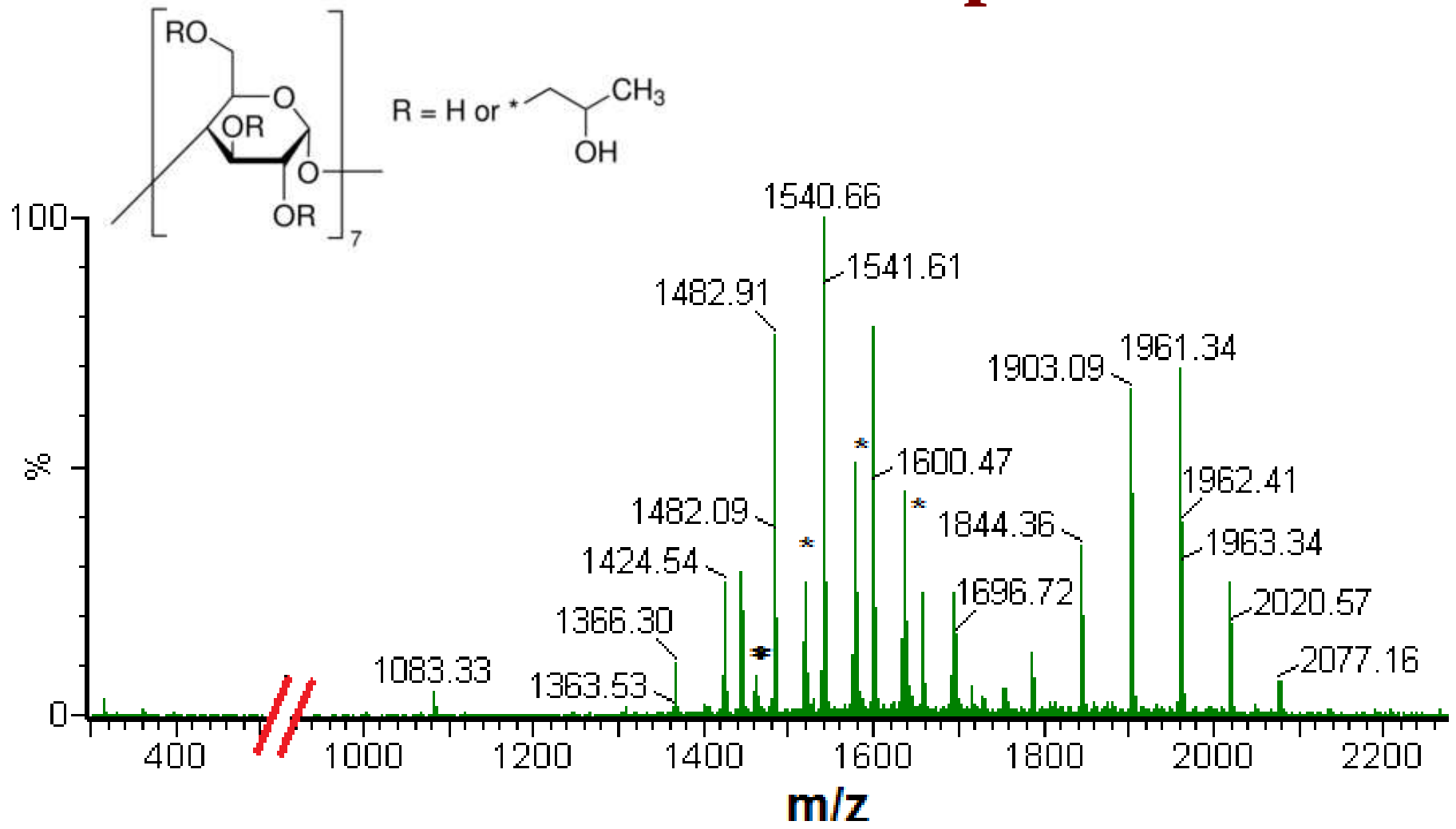
Donor	Acceptor	Occupancy%	Distance (SD)
OH (CD)	OH (BF)	20.4	2.785 (0.11)
OH (CD)	OH (BF)	18.9	2.743 (0.11)
OH (CD)	NH_2 (BF)	16.2	2.868 (0.08)
OH (CD)	NH_2 (BF)	14.8	2.866 (0.08)
OH (CD)	NH_2 (BF)	14.3	2.876 (0.08)

Ofloxacin separation by CE in presence of HPβCD

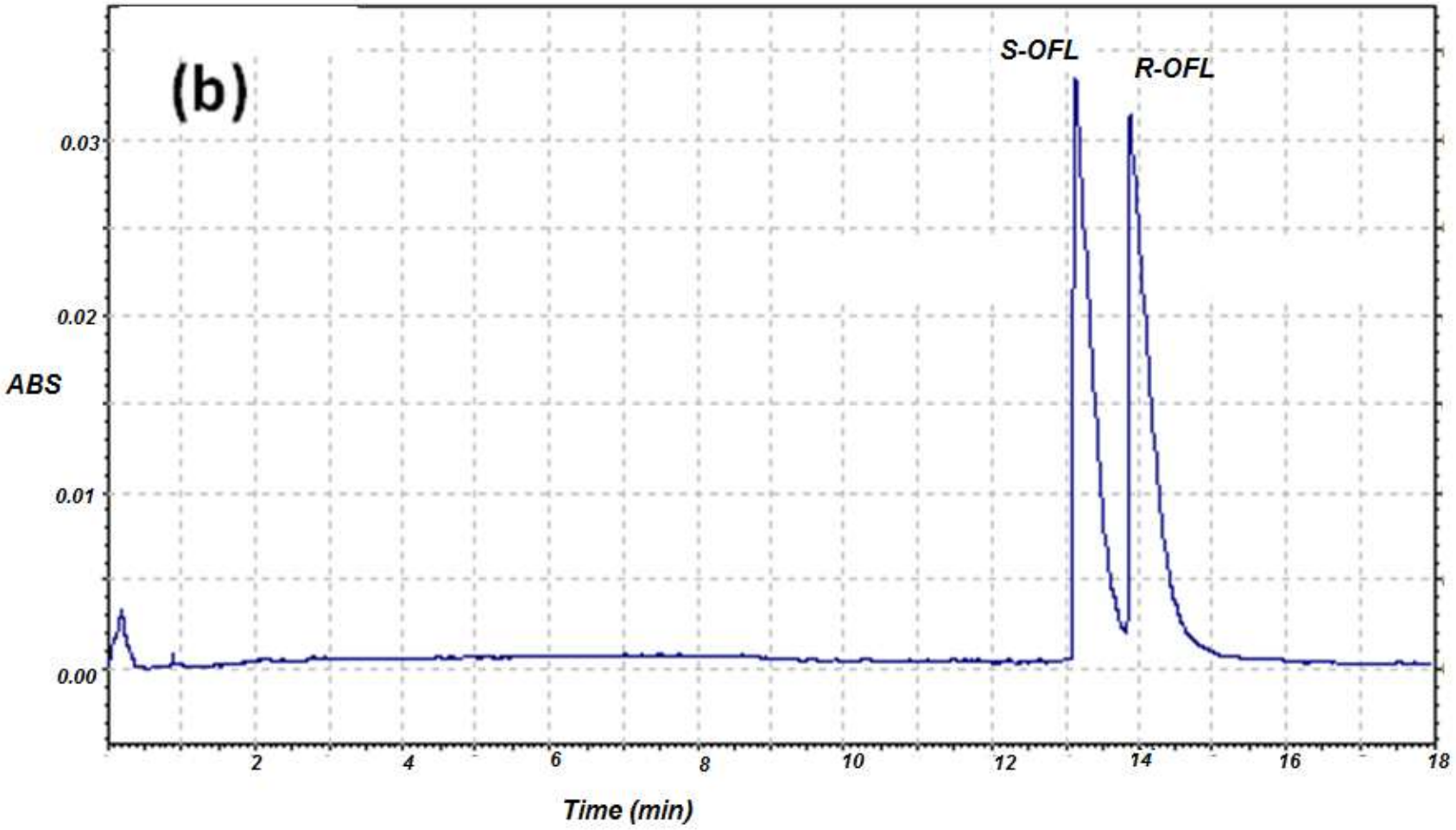


F. O. Suliman , A. A. Elbashir, O. J. Schmitz , *J. Incl. Phenom. Macrocycl. Chemi.* **2015**, 83, 119-129.

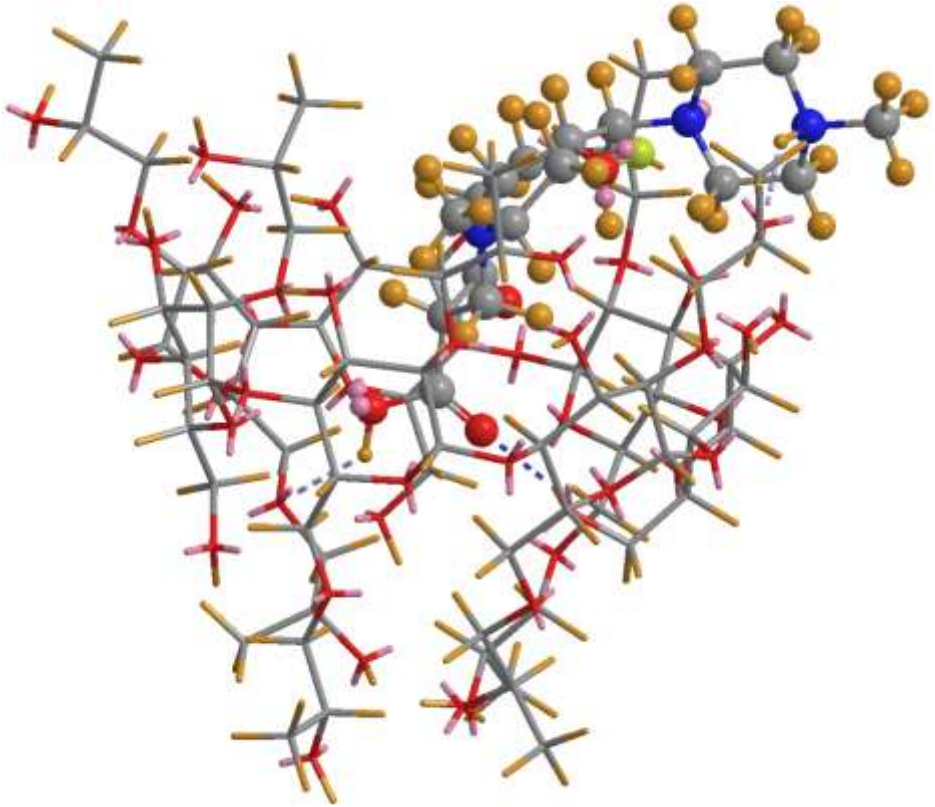
ESI-MS of inclusion complex



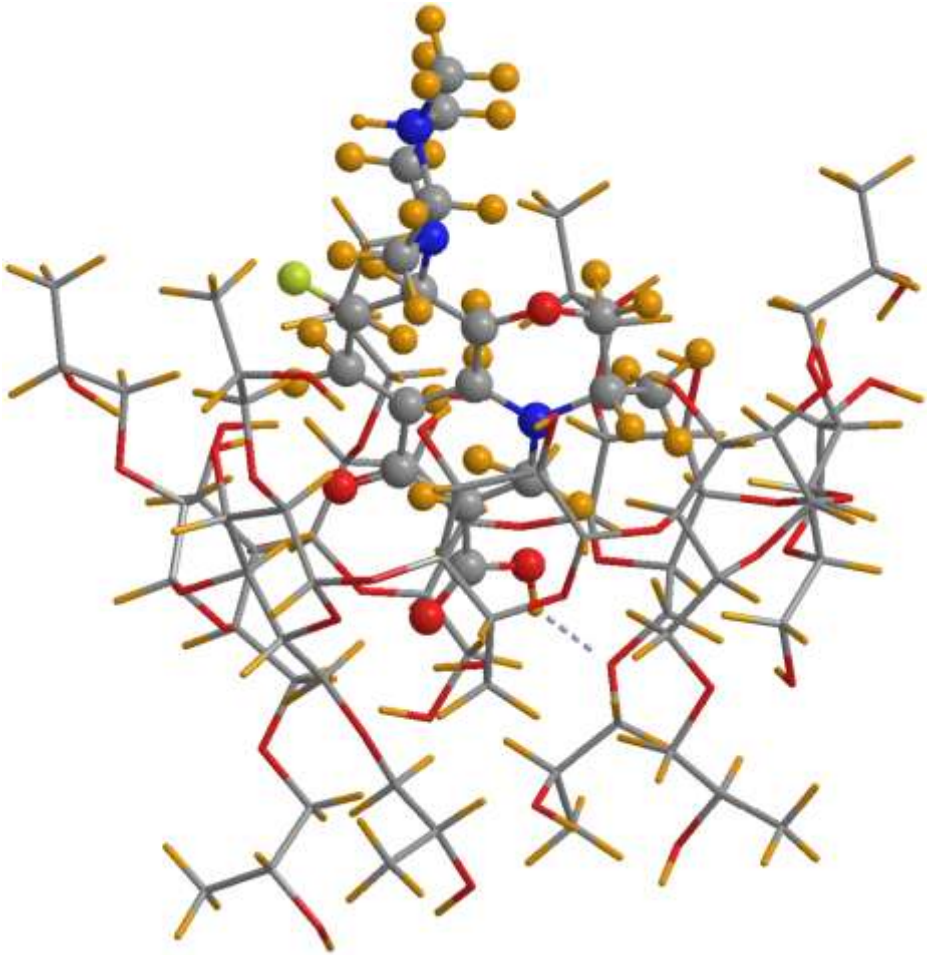
CE-separation



Docking results

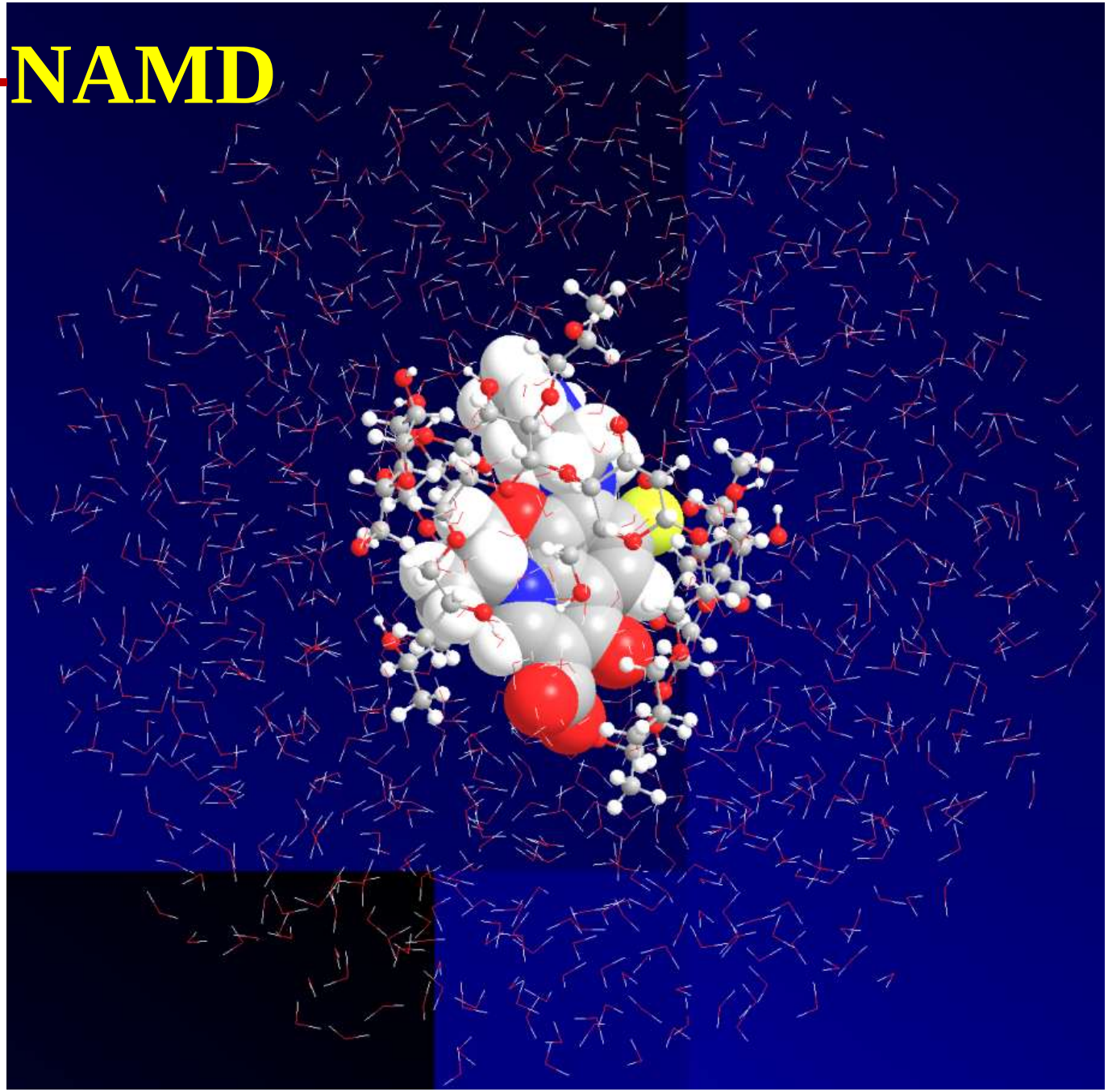


R-OFL

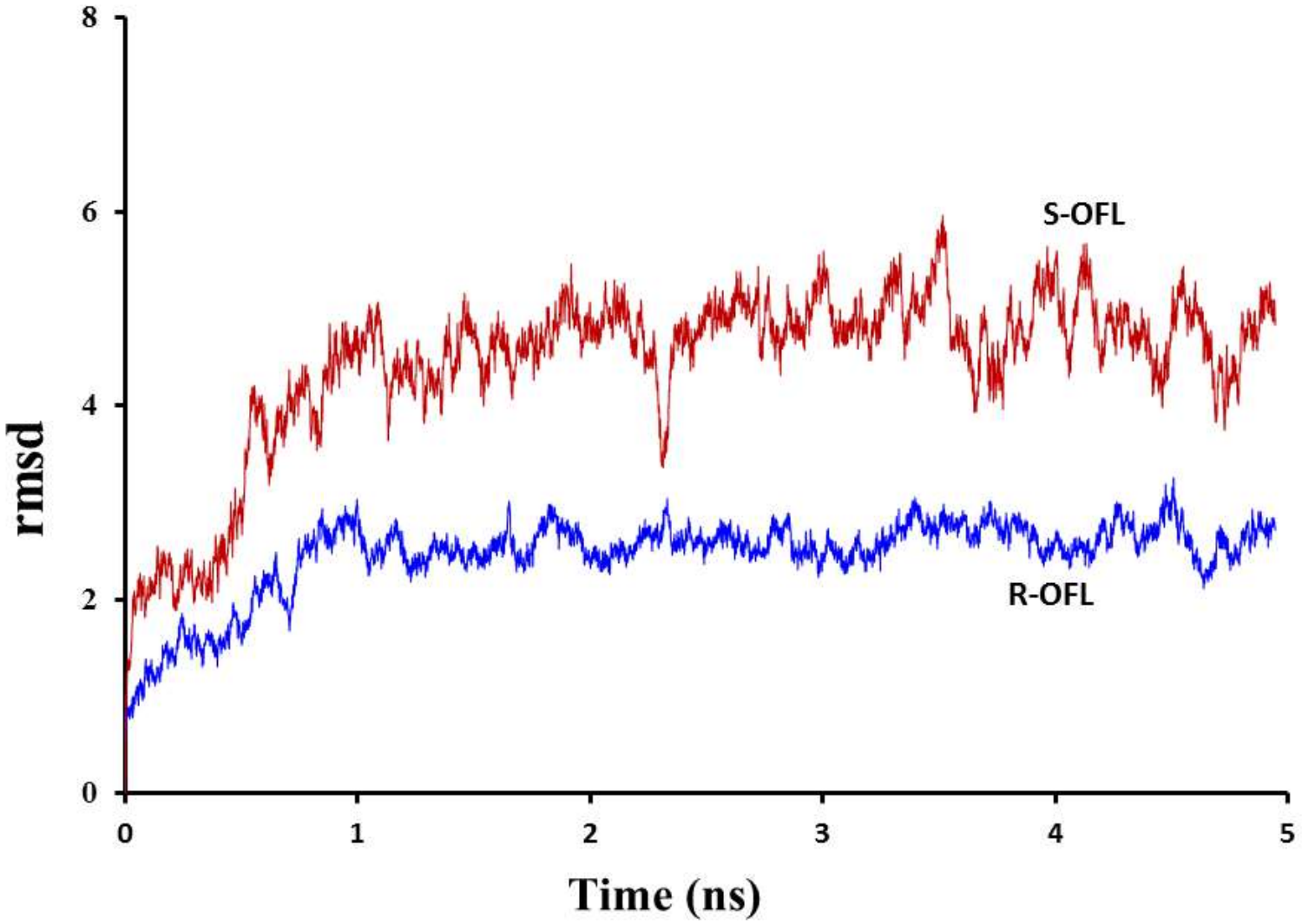


S-OFL

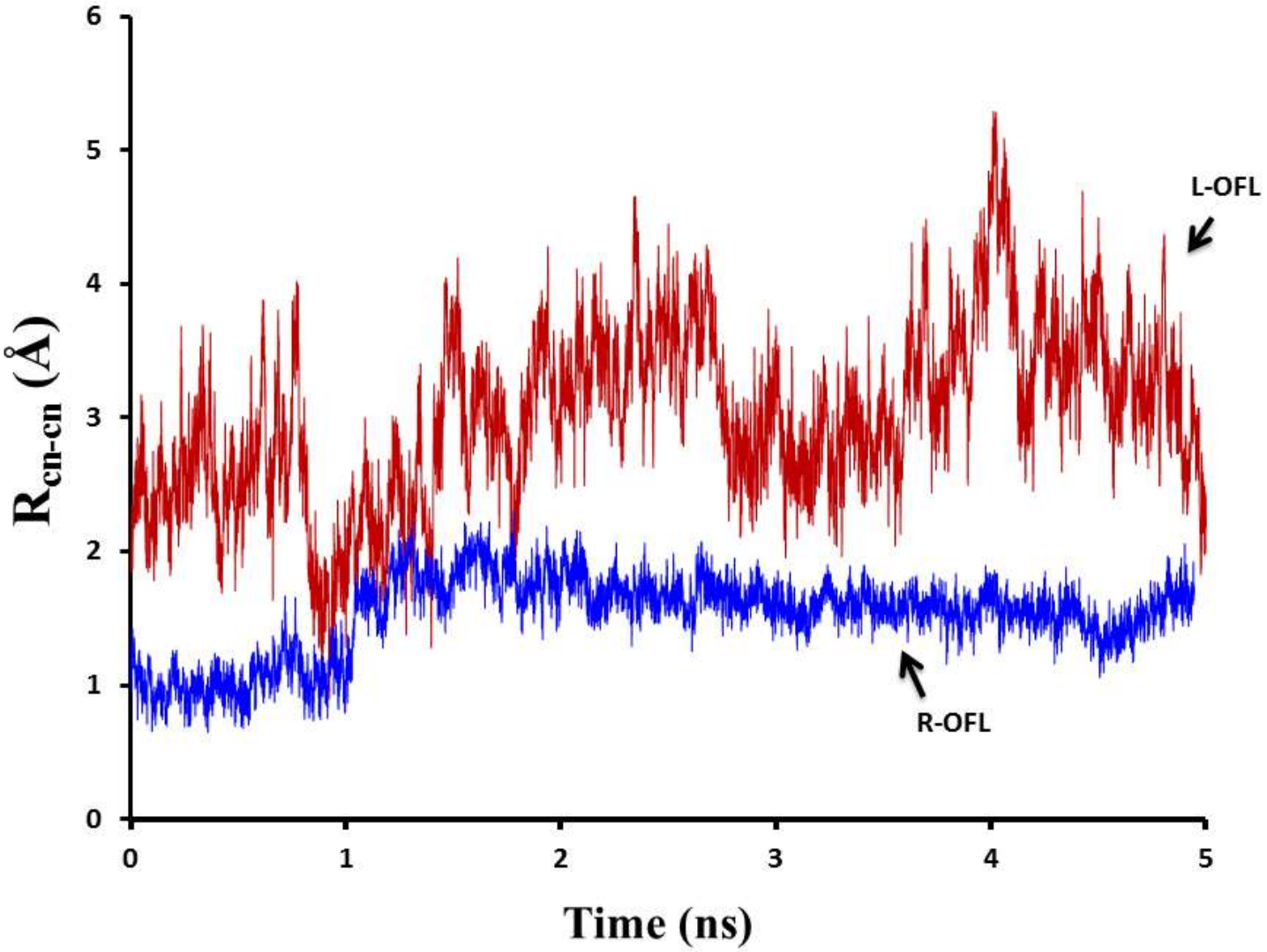
MD-NAMD

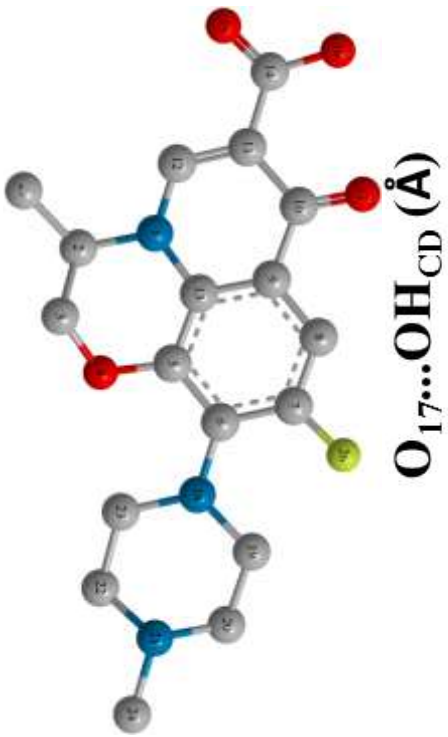


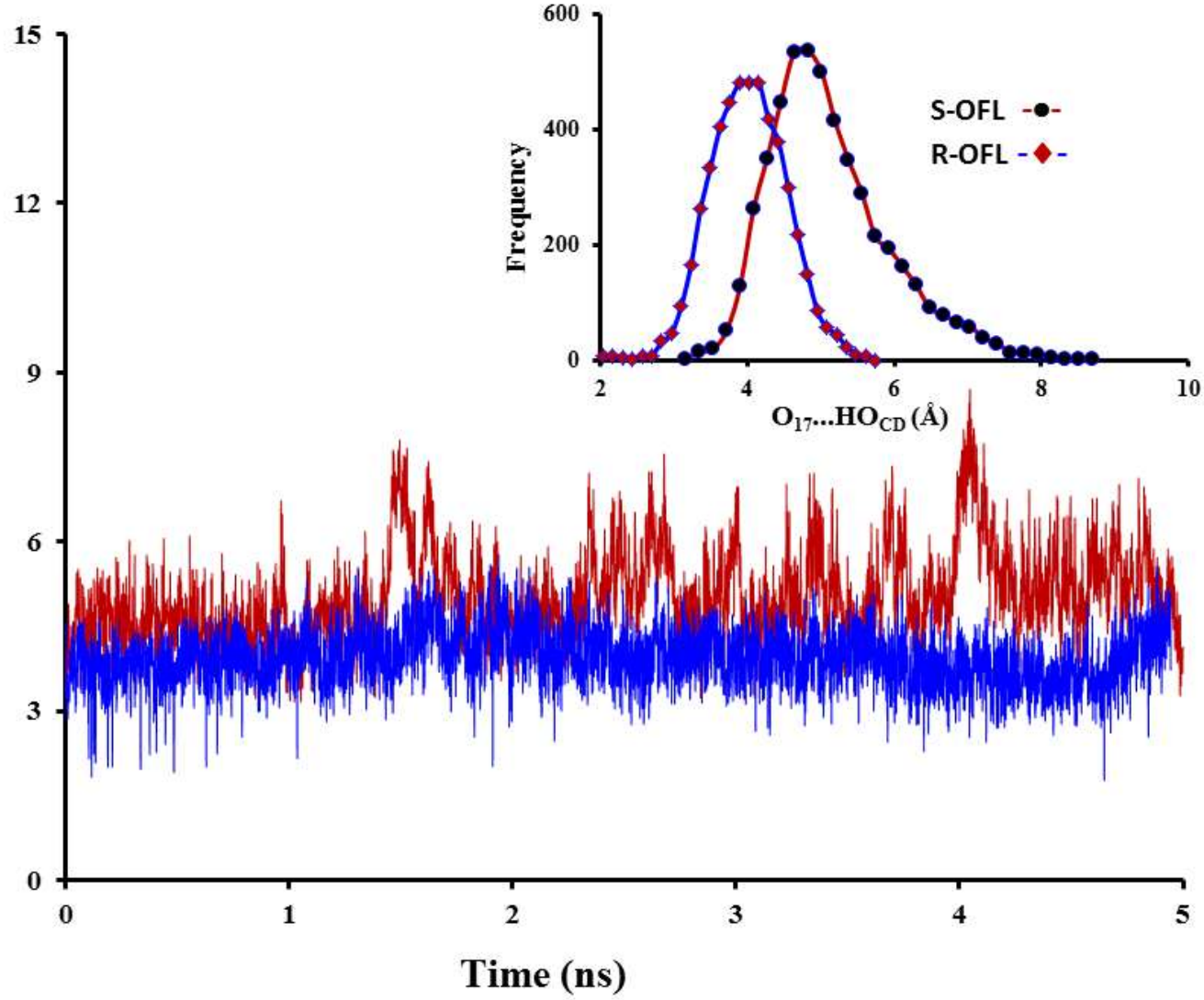
RMSD



R-OFL-HPβCD complex more stable



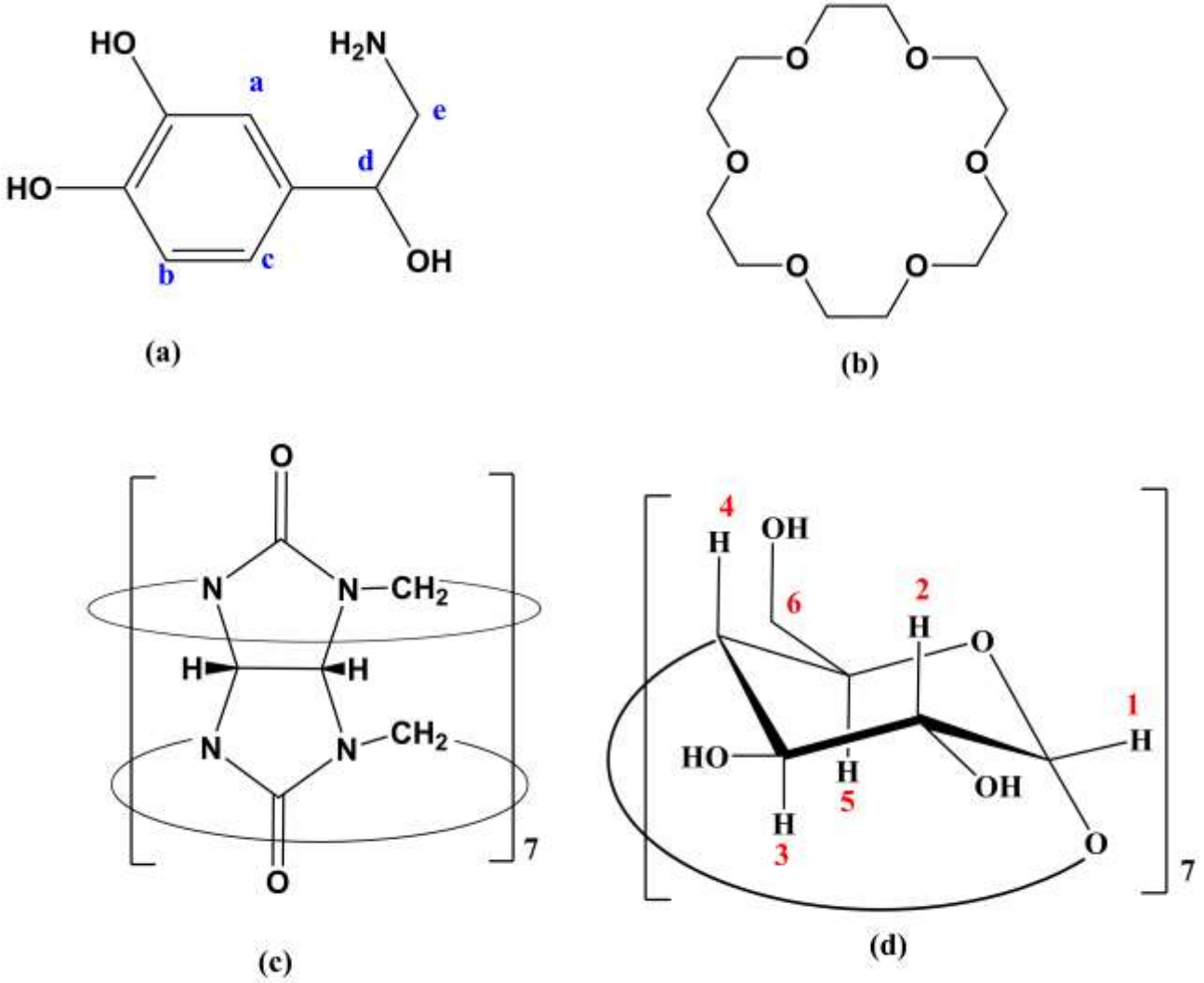



$O_{17}...OH_{CD}$ (Å)
15
12
9
6
3
0
0
1
2
3
4
5
Time (ns)
600
400
200
0
Frequency
2
4
6
8
10
$O_{17}...HO_{CD}$ (Å)
S-OFL
R-OFL

Interaction energies and thermodynamic properties of OFLX-HPβCD inclusion complexes by PM7.

parameter	S- OFLX-HPβCD	R- OFLX-HPβCD
E (kcal mol^{-1})	-2193.0	-2207.0
ΔE(kcal mol^{-1})	-14.5	-29.5
ΔΔE(kcal mol^{-1})	15.0	
ΔH(kcalmol^{-1})	-16.7	-30.3
ΔS(cal $mol^{-1}K^{-1}$)	-41.7	-51.7
ΔG(kcal mol^{-1})	-4.3	-14.9

MD of inclusion complexes of norepinephrine with three hosts: βCD, 18C6 and CB7



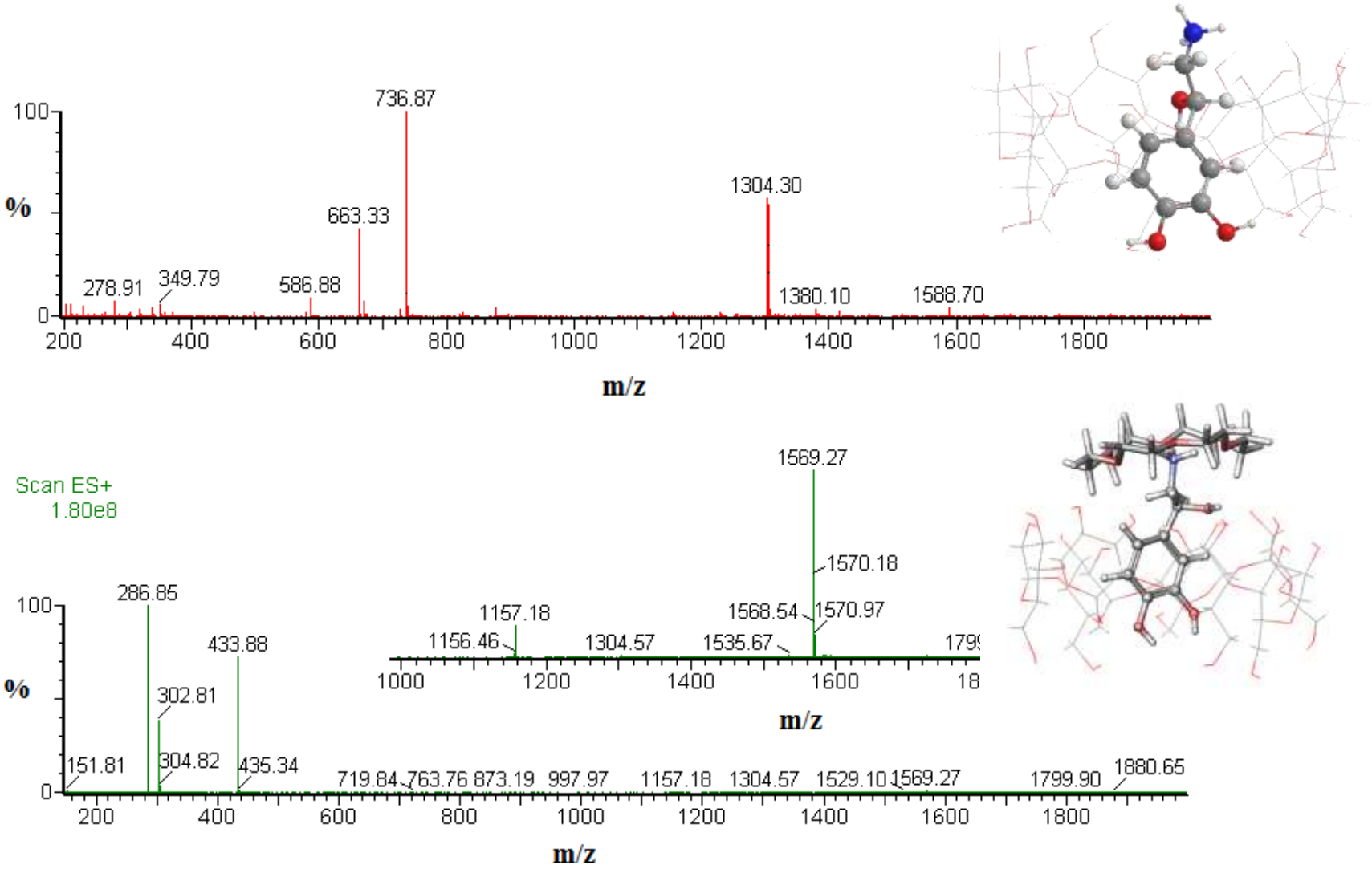
Scheme 1 Structure of guest and hosts. (a) NP (b) 18C6 (c) CB7 (d) βCD

S. K. Al-Burtomani, F. O. Suliman, *RSC Adv*, **2017**, 7, 9888-9902

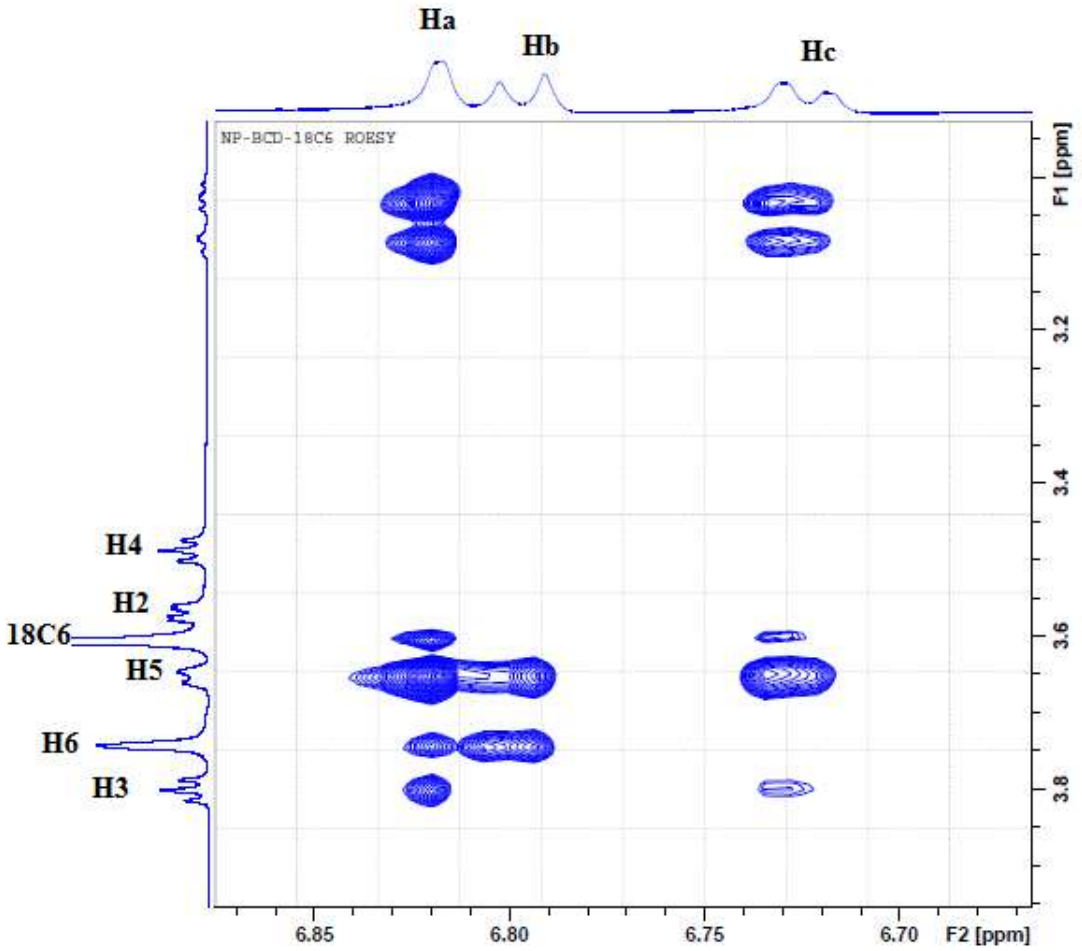
Characterization of complexes

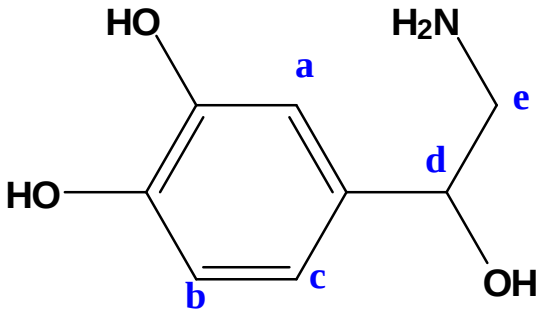
- Fluorescence spectroscopy.
- IR and Raman spectroscopy.
- NMR spectroscopy.
- ESI-Mass spectrometry.
- Powder X-ray crystallography.
- MD calculations.

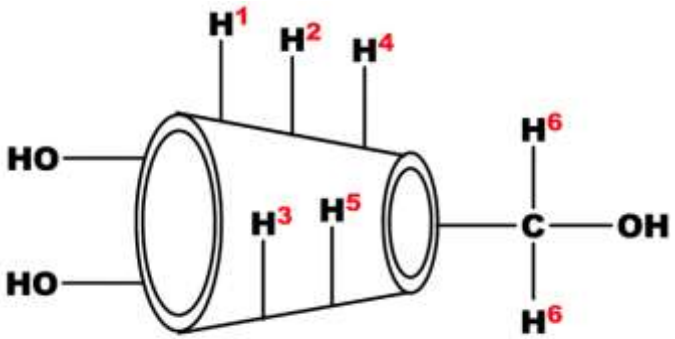
Binary (NPβCD) and ternary complexes (NP-βCD-18C6)

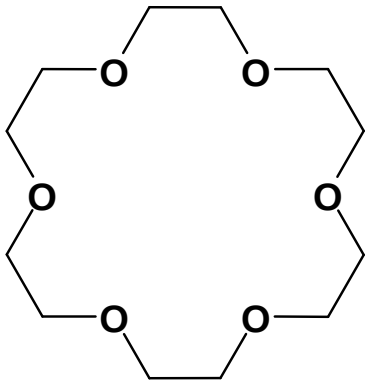


2D NMR


Ha
Hb
Hc
NP-BCD-18C6 ROESY
F1 [ppm]
3.2
3.4
3.6
3.8
H4
H2
18C6
H5
H6
H3
6.85
6.80
6.75
6.70
F2 [ppm]


HO
H2N
a
e
d
HO
c
OH
b


H1
H2
H4
H6
HO
H3
H5
C
OH
HO
H6

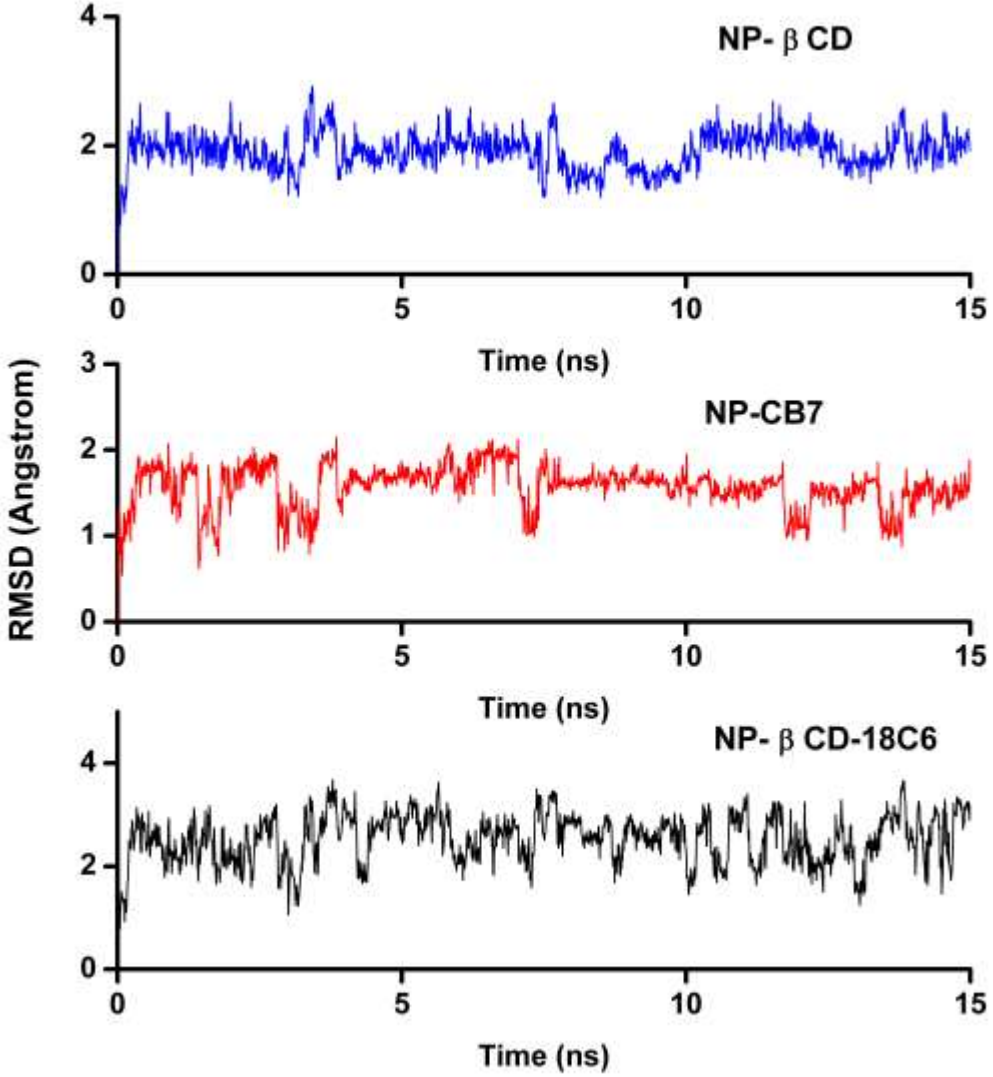

O
O
O
O
O
O

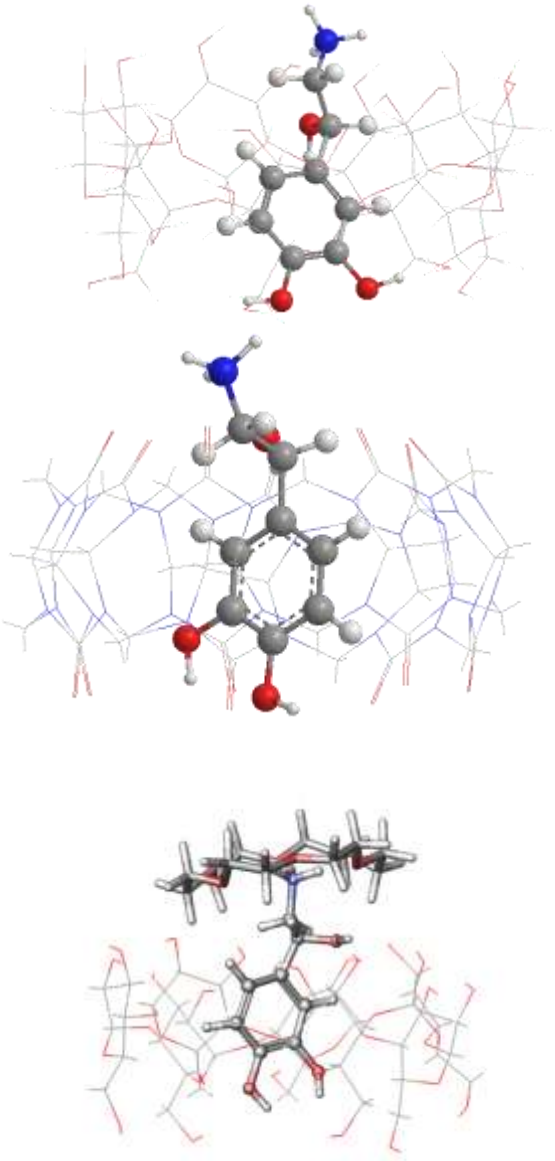
18C6

Binary and ternary complexes: MD calculations

- **Minimization of energy of structurs of guest and hosts**
  - **DFT-B3LYP-6-31G* and PM7**
- **Desmond – Schrodinger-2014 suite (www.schrodinger.com)**
- **OPLS_2005 all atom force field**
  - **Orthorhombic box – TIP3P water.**
  - **Short minimizations on NVT-NPT ensembles**
  - **Production run NPT for 15-20 ns.**

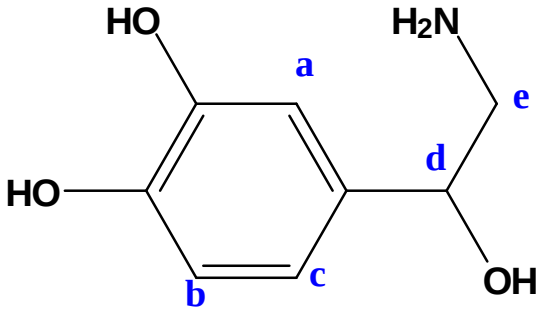
Binary and ternary complexes: MD calculations



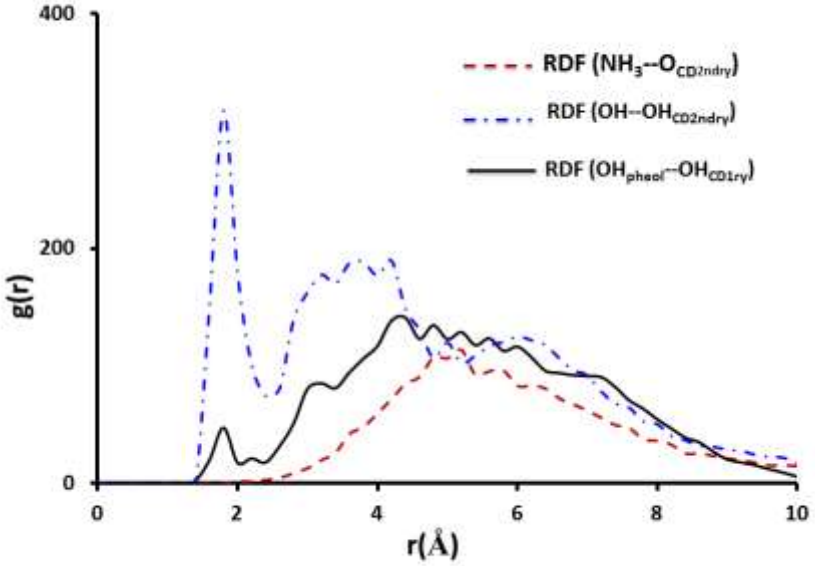


Hydrogen bond analysis

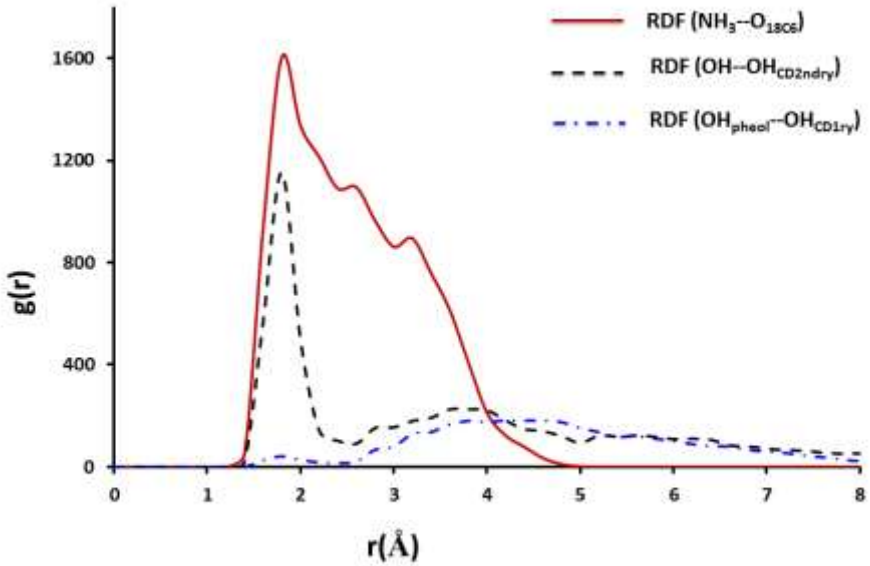
Guest host hydrogen bonding



Binary complex NP- β CD



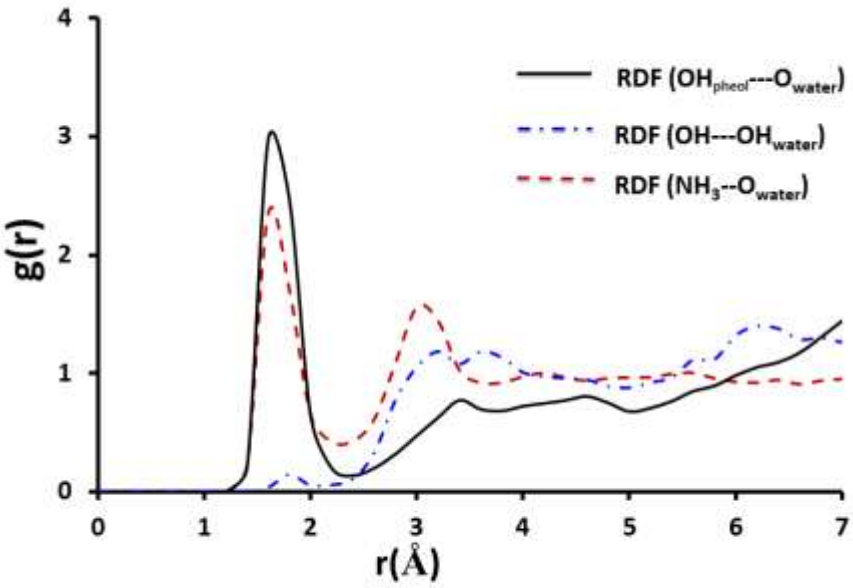
Ternary complex NP-βCD-18C6



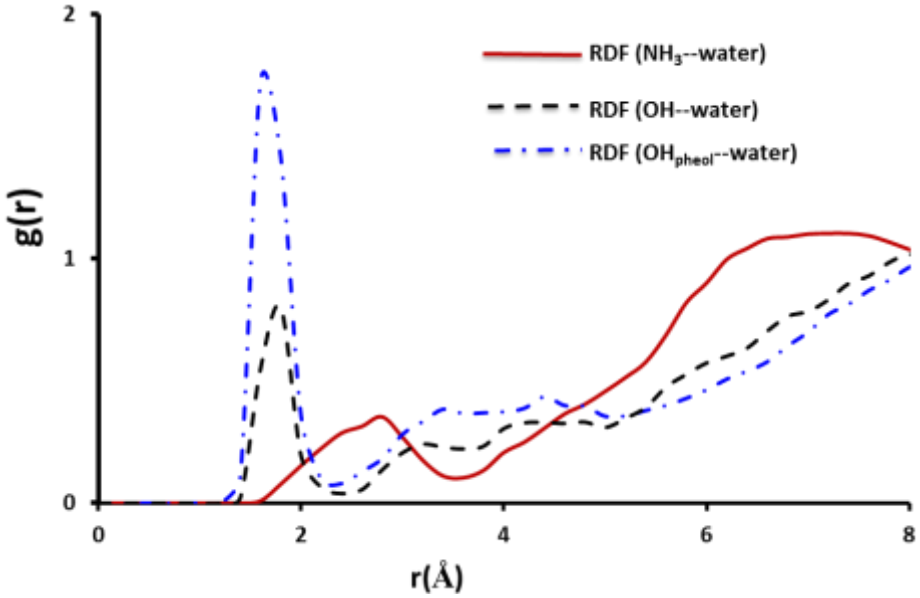
Hydrogen bond analysis

Guest-water hydrogen bonding

Binary complex NP- β CD

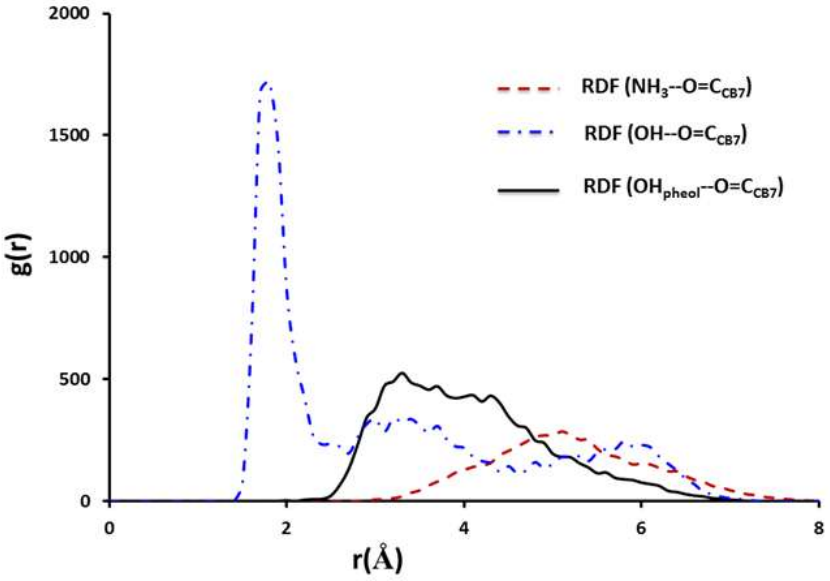


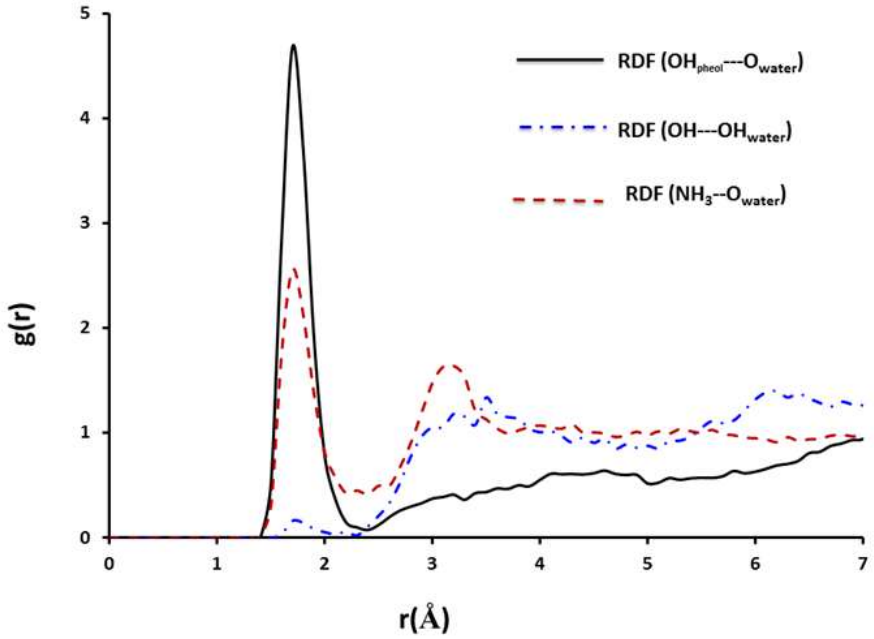
Ternary complex NP-βCD-18C6



NP-CB7 binary complexes

Hydrogen bond analysis





Coclusion

- **Molecular modeling helped in understanding the mechanisms of separation.**
- **The calculated energies predicted the experimental behavior to a reasonable extent.**
- **There are many potential applications for theoretical calculations.**

Current and future work

- **Use of molecular dynamic to simulate the formation of ternary complexes (2-hosts and one guest).**
- **Molecular dynamic simulation of interaction of steroids with cucurbit[n]urils.**
- **Computation of free energy: Umbrella sampling, Adaptively Biased Molecular Dynamics, Metadynamic methods, etc..**

Acknowledgement

- **SQU: for financial support.**