

# Cyclohexanohemicucurbit[8]uril - a Neutral Host for Anionic Guests

Sandra Kaabel<sup>a</sup>, Jasper Adamson<sup>b</sup>, Elina Kalenius<sup>c</sup>, Anniina Kiesilä<sup>c</sup>, Filip Topić<sup>c</sup>, Mario Öeren<sup>a</sup>, Elena Prigorchenko<sup>a</sup>, Mart Reimund<sup>a</sup>, Aivar Lõokene<sup>a</sup>, Kari Rissanen<sup>c</sup> and Riina Aav<sup>a</sup>

<sup>a</sup> Department of Chemistry, Tallinn University of Technology Akadeemia tee 15, 12618 Tallinn, Estonia

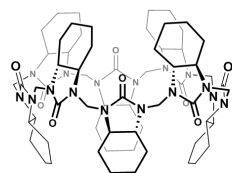
<sup>b</sup> National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia

<sup>c</sup> University of Jyväskylä, Department of Chemistry, P.O. Box. 35, 40014 Jyväskylä, Finland

E-mail: sandra.kaabel@ttu.ee

## Introduction

Anion binding receptors in polar solvents are challenged by the energy cost of anion desolvation and the competitive nature of the solvent to the receptor binding sites.<sup>1</sup> Hemicucurbit[*n*]urils (HC[*n*]s) are neutral macrocyclic host molecules which preferentially bind anionic guests.<sup>2</sup> Chiral cyclohexanohemicucurbit[*n*]urils (cycHC[*n*]) have been studied by our group.<sup>3,4</sup>



cycHC[8]

The strong and selective binding of (*all-R*)-cycHC[8] with a number of anions in protonic solvents is explored by single crystal XRD, NMR spectroscopy, isothermal titration calorimetry, ESI mass spectrometry and computational chemistry methods.

## Scope of complexing anions by ESI-MS

**Binding:** PF<sub>6</sub><sup>-</sup>, SbF<sub>6</sub><sup>-</sup>, ClO<sub>4</sub><sup>-</sup>, ReO<sub>4</sub><sup>-</sup>, SCN<sup>-</sup>, BF<sub>4</sub><sup>-</sup>, HSO<sub>4</sub><sup>-</sup>, CF<sub>3</sub>SO<sub>3</sub><sup>-</sup>, OAc<sup>-</sup>, H<sub>2</sub>PO<sub>4</sub><sup>-</sup>, IO<sub>4</sub><sup>-</sup>, N(CN)<sub>2</sub><sup>-</sup>, IO<sub>3</sub><sup>-</sup>

**Weakly binding:** Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, NO<sub>3</sub><sup>-</sup>, NO<sub>2</sub><sup>-</sup>

**Non-binding:** B(CN)<sub>4</sub><sup>-</sup>, CH<sub>3</sub>BF<sub>3</sub><sup>-</sup>, CH<sub>3</sub>CH<sub>2</sub>BF<sub>3</sub><sup>-</sup>, CN<sup>-</sup>, AuBr<sub>4</sub><sup>-</sup>, Br<sub>3</sub><sup>-</sup>, F<sup>-</sup>

**Relative affinity ranking (G1:G2:cycHC[8] competition experiments)**

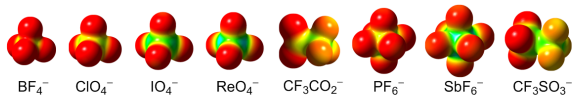
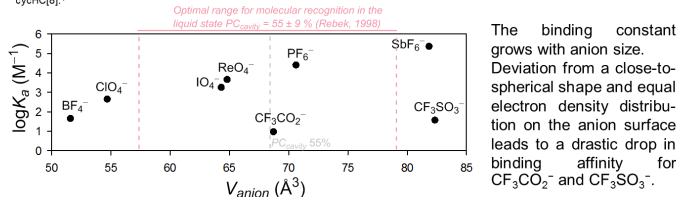
SbF<sub>6</sub><sup>-</sup> = PF<sub>6</sub><sup>-</sup> >> ClO<sub>4</sub><sup>-</sup> = ReO<sub>4</sub><sup>-</sup> >> SCN<sup>-</sup> >> BF<sub>4</sub><sup>-</sup> > HSO<sub>4</sub><sup>-</sup> >> CF<sub>3</sub>SO<sub>3</sub><sup>-</sup> >> H<sub>2</sub>PO<sub>4</sub><sup>-</sup> > OAc<sup>-</sup>

## NMR spectroscopy and isothermal titration calorimetry

The 1:1 stoichiometry of complexation of anionic guests (G) with cycHC[8] (H) in methanol was determined using the Job's method of continuous variation. NMR titration experiments revealed the strongest binding for SbF<sub>6</sub><sup>-</sup>.

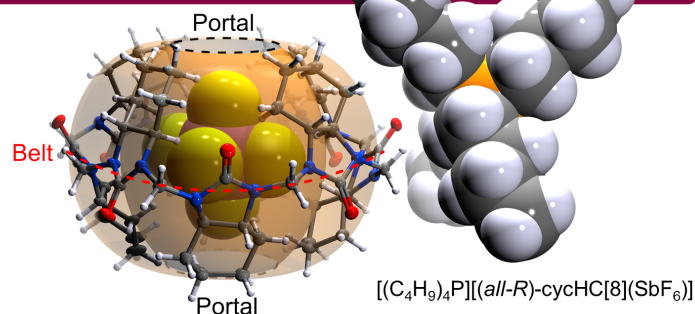
Anion	Cation	Solvent	V <sub>guest</sub> (Å <sup>3</sup> )	PC <sub>cavity</sub> (%)	K <sub>a</sub> (M <sup>-1</sup> )
SbF <sub>6</sub> <sup>-</sup>	Na <sup>+</sup>	MeOD	81.8	66.5	(2.5±0.7) · 10 <sup>5</sup>
PF <sub>6</sub> <sup>-</sup>	Bu <sub>4</sub> N <sup>+</sup>	MeOD	70.6	57.4	(2.8±0.4) · 10 <sup>4</sup>
PF <sub>6</sub> <sup>-</sup>	Bu <sub>4</sub> N <sup>+</sup>	1:1 MeOD/D <sub>2</sub> O	70.6	57.4	(2.6±0.2) · 10 <sup>4</sup>
PF <sub>6</sub> <sup>-</sup>	Na <sup>+</sup>	MeOD	70.6	57.4	(2.0±0.2) · 10 <sup>4</sup>
ReO <sub>4</sub> <sup>-</sup>	Bu <sub>4</sub> N <sup>+</sup>	MeOD	64.8	52.7	(4.7±0.4) · 10 <sup>3</sup>
IO <sub>4</sub> <sup>-</sup>	Na <sup>+</sup>	MeOD	64.3	52.3	(1.8±0.2) · 10 <sup>3</sup>
ClO <sub>4</sub> <sup>-</sup>	Bu <sub>4</sub> N <sup>+</sup>	MeOD	54.7	44.5	(4.7±0.2) · 10 <sup>2</sup>
BF <sub>4</sub> <sup>-</sup>	Bu <sub>4</sub> N <sup>+</sup>	MeOD	51.6	42.0	(4.8±0.4) · 10
CF <sub>3</sub> SO <sub>3</sub> <sup>-</sup>	Bu <sub>4</sub> N <sup>+</sup>	MeOD	82.3	66.9	(3.9±0.5) · 10
CF <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	Bu <sub>4</sub> N <sup>+</sup>	MeOD	68.7	55.8	< 10

<sup>1</sup> V<sub>guest</sub> is based on optimized anion geometries (BP86-D/def2-TZVPD) and calculated using CSD default atomic radii.  
<sup>2</sup> PC<sub>cavity</sub> defined as the ratio (%) between the V<sub>guest</sub> to V<sub>cavity(host)</sub>: V<sub>cavity</sub>(cycHC[8]) = 123.0 Å<sup>3</sup>, measured from the crystal structure of cycHC[8].

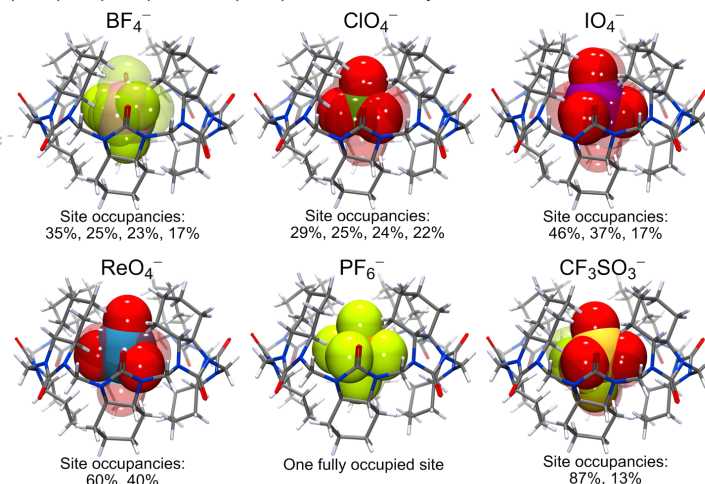


Guest	K <sub>a</sub> (M <sup>-1</sup> ) by ITC	ΔH° (kJ/mol)	TΔS° (kJ/mol)	ΔG° (kJ/mol) ITC	ΔG° (kJ/mol) DFT
NaSbF <sub>6</sub>	(1.02±0.03) · 10 <sup>5</sup>	-56.2±0.3	-27.7	-28.6	-
NaPF <sub>6</sub>	(1.29±0.04) · 10 <sup>4</sup>	-43.8±0.2	-20.3	-23.5	-22

## Single Crystal X-ray Diffraction Analysis

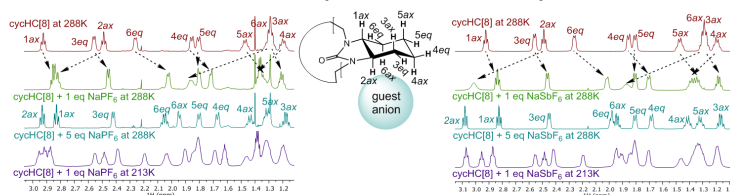


A series of isomorphous single crystals of anion inclusion complexes with cycHC[8] were obtained from methanol, using either tetrabutylammonium (TBA) or -phosphonium (TBP) salts for the crystallizations.



## Low temperature NMR

Guest exchange is fast on NMR timescale at room temperature. Coalescence temperature for PF<sub>6</sub><sup>-</sup> is 241 K and for SbF<sub>6</sub><sup>-</sup> 253 K.



## DFT model for the complexation

A single molecule of methanol occupies the cycHC[8] cavity at temperatures over 100K. Upon guest complexation the methanol is pushed towards the opposite portal, breaking the weak hydrogen bond between the solvent molecule and the host cavity. Follow the QR code for a video on the complexation reaction pathway.



## Conclusions

- Complexation of a number of anions with cycHC[8] is confirmed in gas phase, solution and solid state.
- Binding to cycHC[8] is size and shape selective, with octahedral SbF<sub>6</sub><sup>-</sup> showing highest binding affinity K<sub>a</sub> = 250 000 M<sup>-1</sup>.
- The binding of octahedral and tetrahedral anions with cycHC[8] grows by the orders of magnitude with the increasing size of the guest.
- Deviations in shape and electron-density distribution of the anion result in weak binding.
- The complexation is enthalpy driven, outweighing the unfavourable entropy changes. Guest exchange is fast on the NMR timescale.

## References

1. M. J. Langton, C. J. Serpell, P. D. Beer, *Angew. Chem. Int. Ed.* **2016**, *55* (6), 1974–1987
2. Y. Miyahara, K. Goto, M. Oka, T. Inazu, *Angew. Chem., Int. Ed.* **2004**, *43*, 5019.
3. R. Aav, E. Shmatova, I. Reile, M. Borissova, F. Topić, K. Rissanen, *Org. Lett.* **2013**, *15* (14), 3786–3789.
4. E. Prigorchenko, M. Öeren, S. Kaabel, M. Fomitsenko, I. Reile, I. Jarving, T. Tamm, F. Topić, K. Rissanen, R. Aav, *Chem. Commun.* **2015**, 10921.
5. S. Mecozić, J. J. Rebek, *Chem. - A Eur. J.*, **1998**, *4*, 1016–1022

## Acknowledgements

The authors would like to thank Mari-Liis Kasemets (Tallinn University of Technology) and Marina Kudrjašova for experimental assistance with NMR analysis and Lauri Kivijärvi (University of Jyväskylä) for his assistance with ESI-TOF MS.