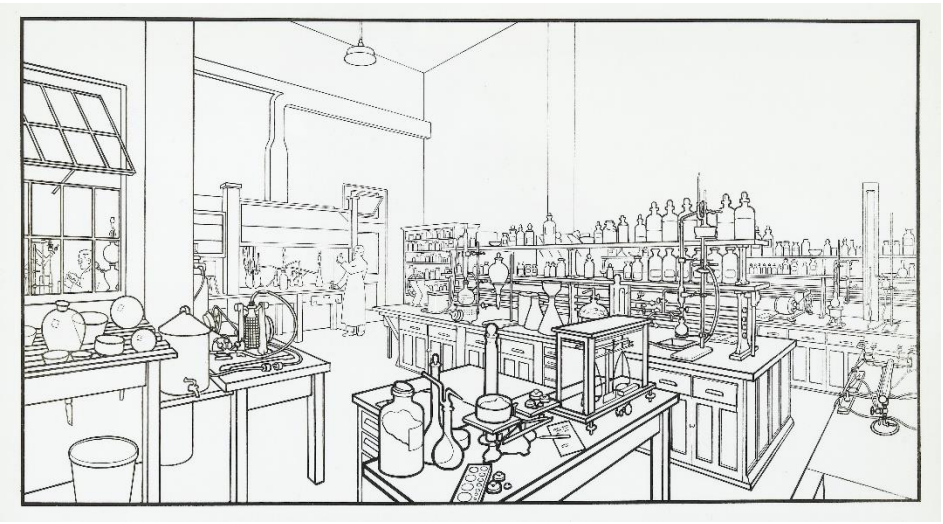
On the interface between experiment and computation, the experimentalists viewpoint

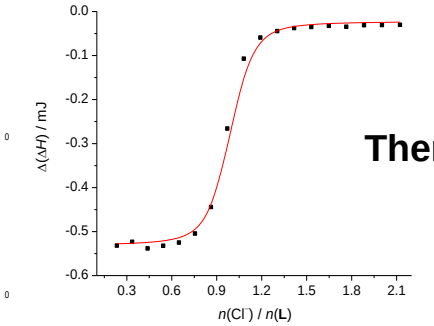


Gordan Horvat

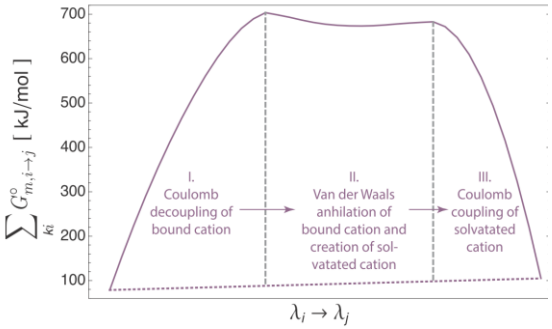
Department of Chemistry, Faculty of Science,
University of Zagreb

Observation

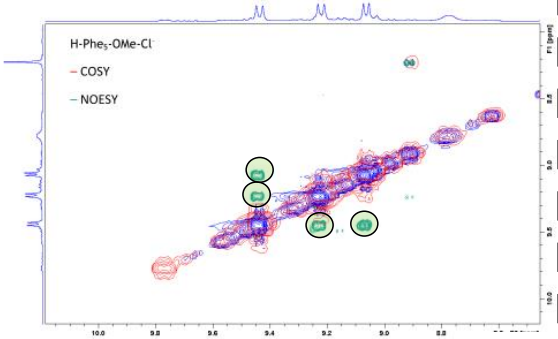
Microcalorimetry

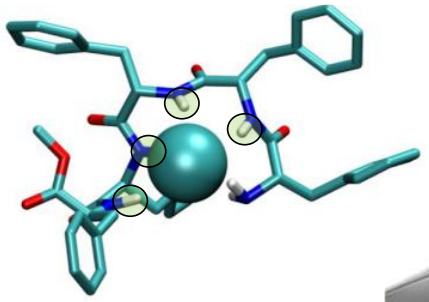


Thermodynamics



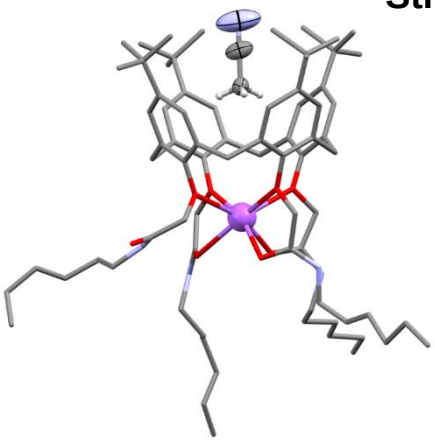
NMR Spectroscopy

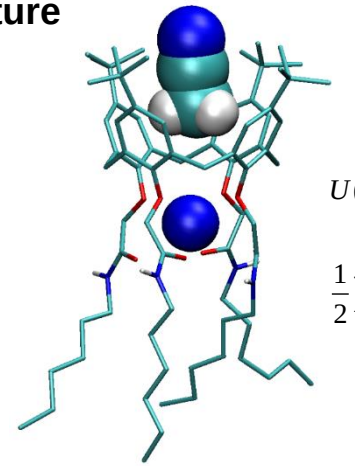




Structure

X-ray Crystallography





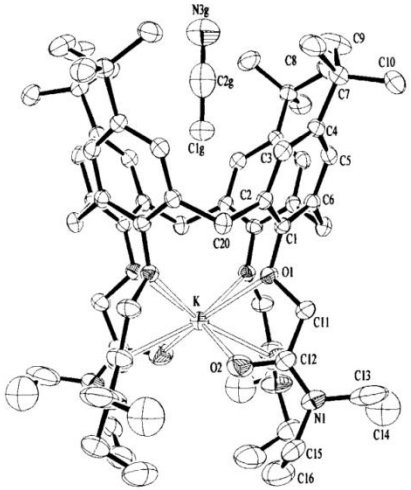
Modelling

$$U(\mathbf{r}_N) = \sum_{bonds} K_r (r_i - r_{eq})^2 + \sum_{angles} K_\varphi (\theta_i - \theta_{eq})^2 + E_{torsions} +$$

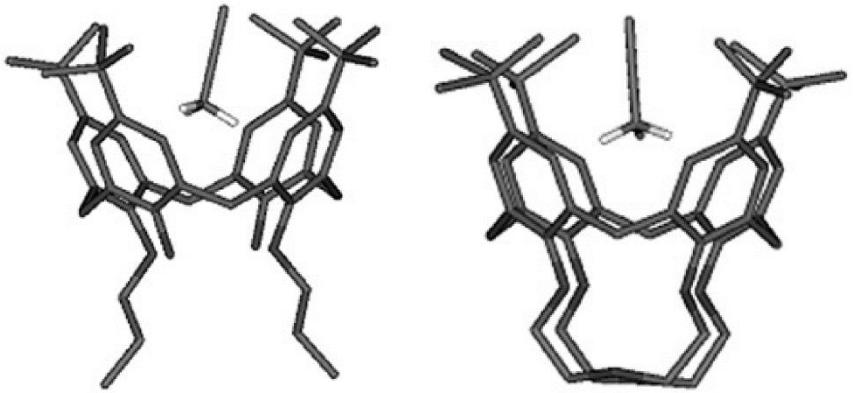
$$\frac{1}{2}\sum_{i=1}^{N}\sum_{j=1,j\neq i}^{N}\frac{q_i q_j}{4\pi\varepsilon_0 d_{ij}} + \frac{1}{2}\sum_{i=1}^{N}\sum_{j=1,j\neq i}^{N} 4\varepsilon_{ij}\left(\left(\frac{\sigma_{ij}}{d_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{d_{ij}}\right)^{6}\right)$$

Classical MD simulations

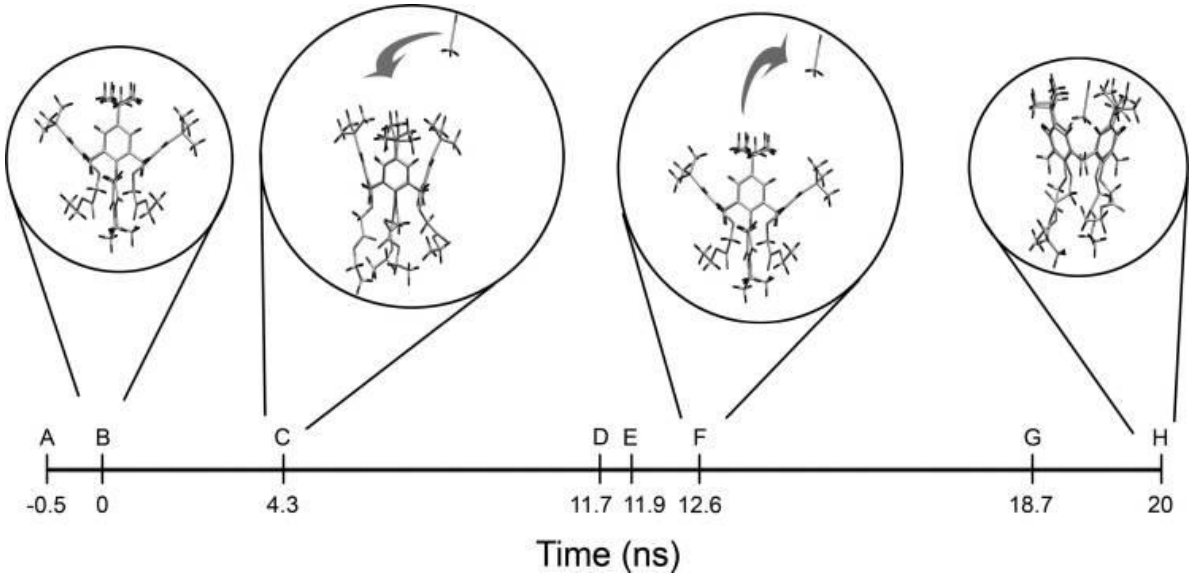
Calix[4]arene cation complexes, PhD thesis



Arduini et al., *Tetrahedron* **57** (2001) 2411–2417.

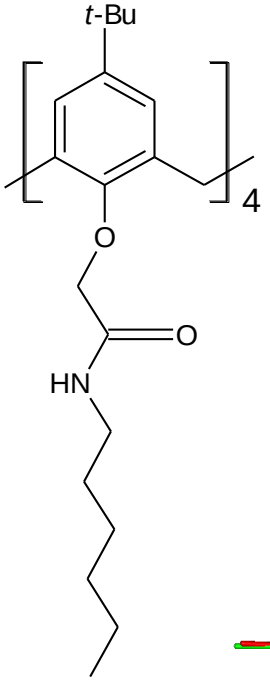


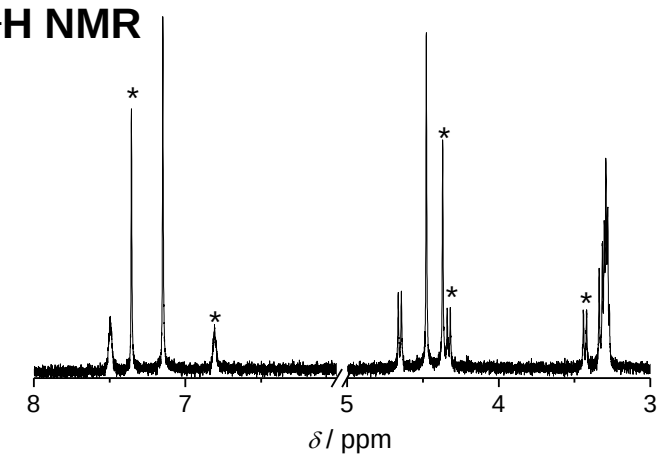
Arena et al., *New J. Chem.* **28** (2004) 56–61.

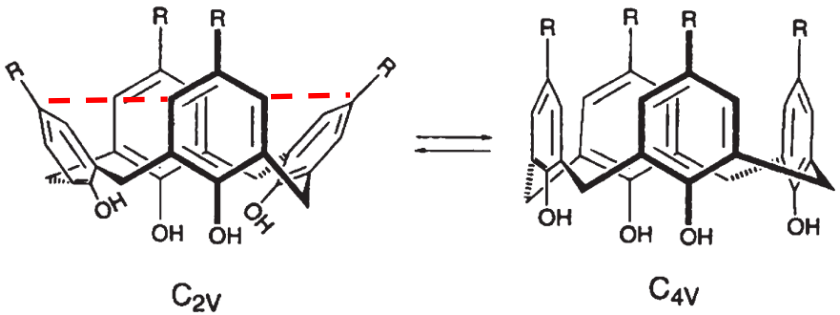


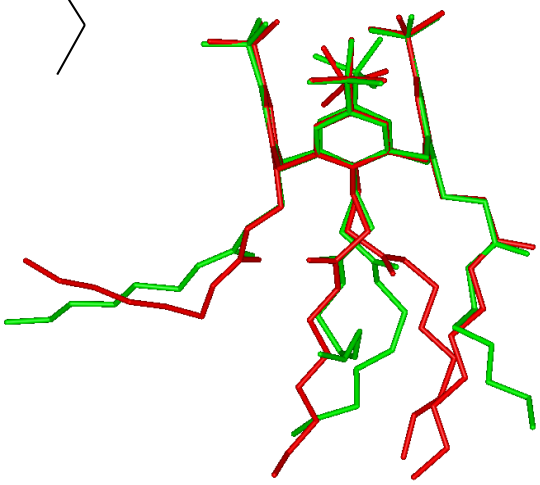
A. S. de Araujo, O. E. Piro, E. E. Castellano, A. F. Danil de Namor, *J. Phys. Chem. A* **112** (2008) 11885–11894.

Free calix[4]arene in acetonitrile

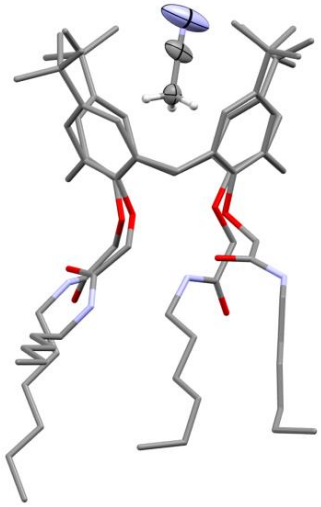




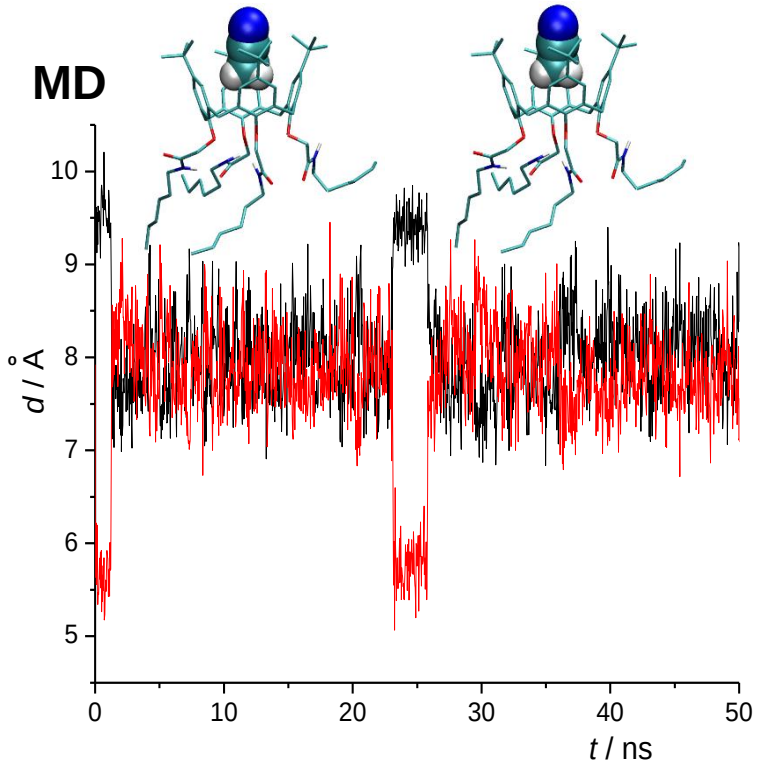




Free: X-ray vs MD

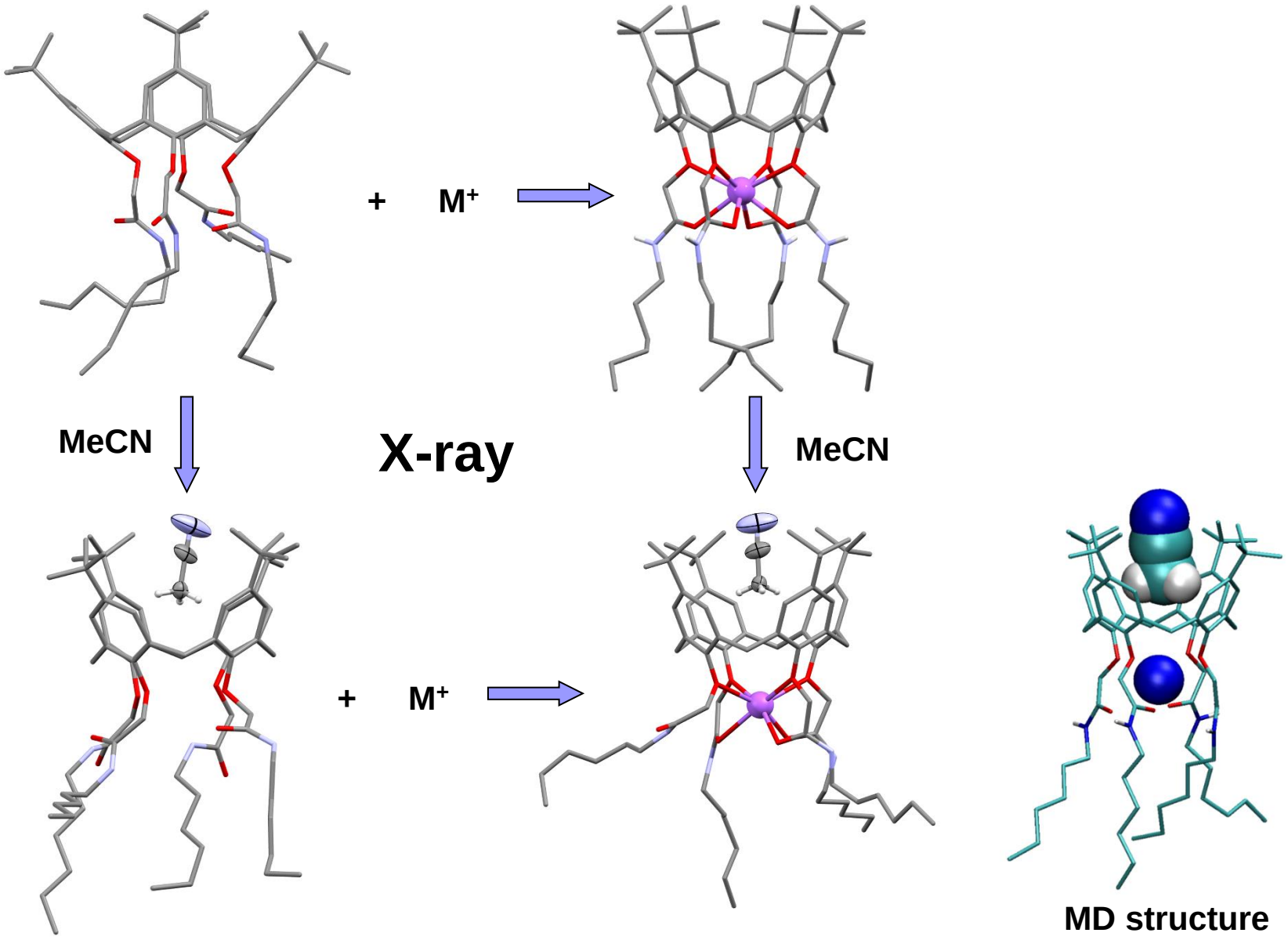


MeCN adduct: X-ray



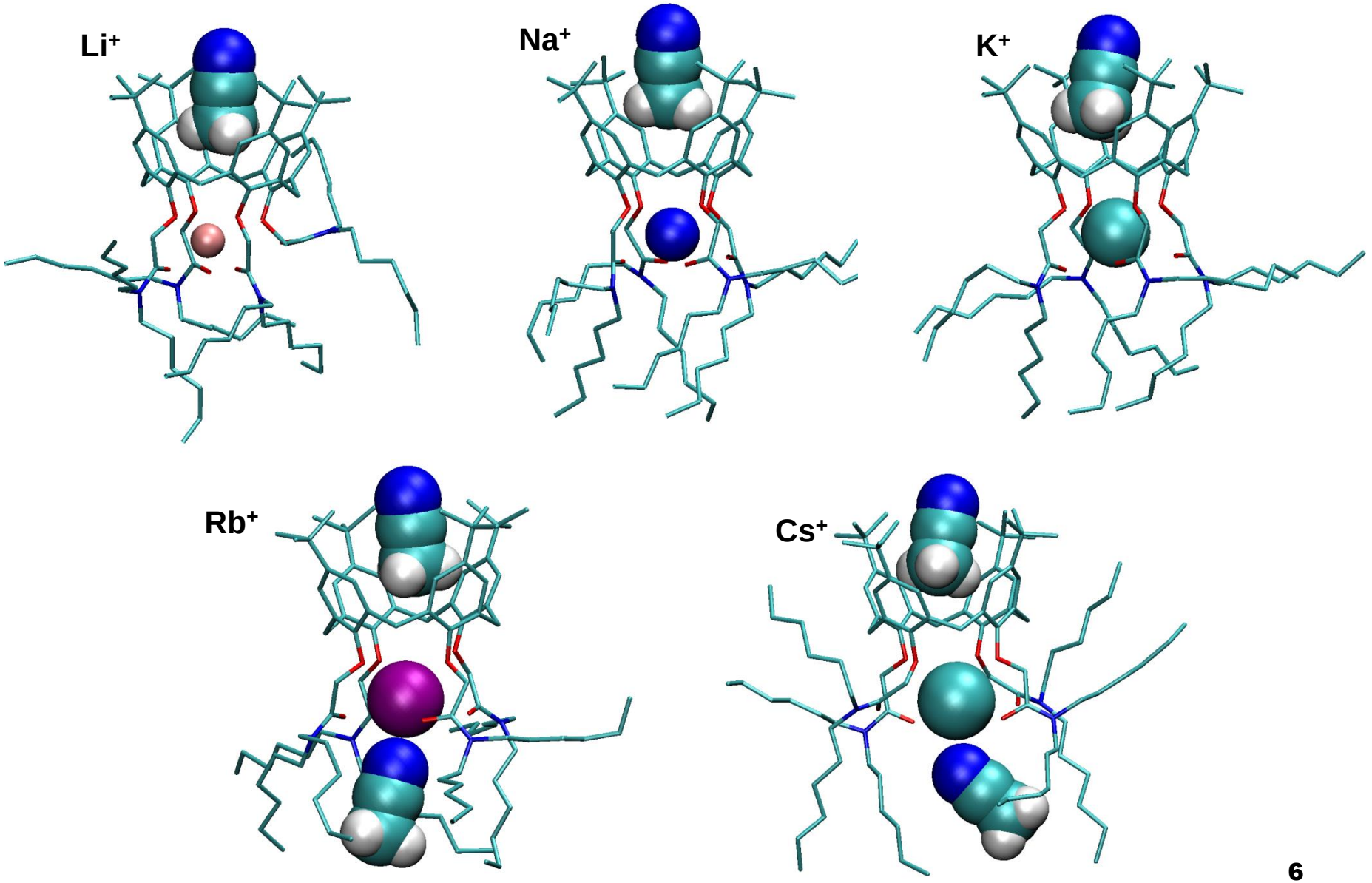
G. Horvat, V. Stilinović, T. Hrenar, B. Kaitner, L. Frkanec, V. Tomišić, *Inorg. Chem.* **51** (2012) 6264–6278.

Crystal structure vs MD



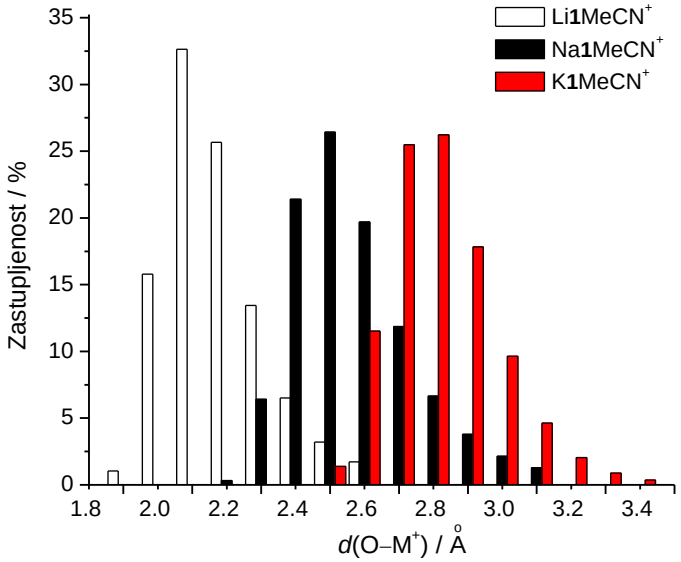
G. Horvat, V. Stilinović, T. Hrenar, B. Kaitner, L. Frkanec, V. Tomišić, *Inorg. Chem.* **51** (2012) 6264–6278.

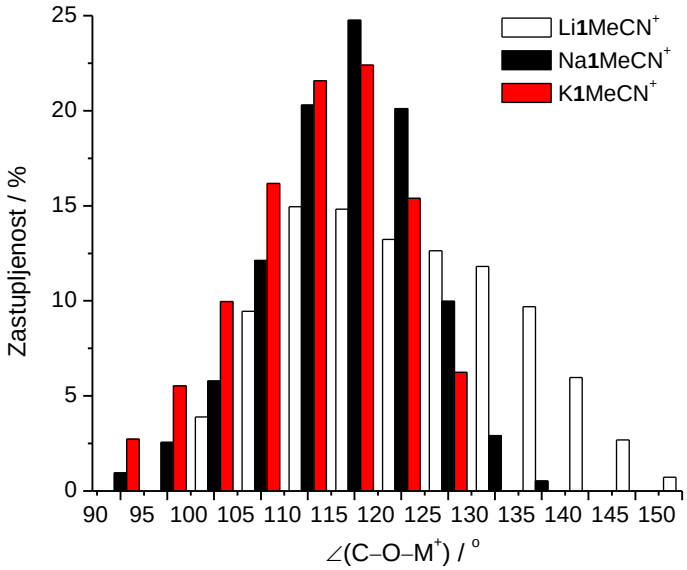
MD structures of M^+ calix[4]arene complexes



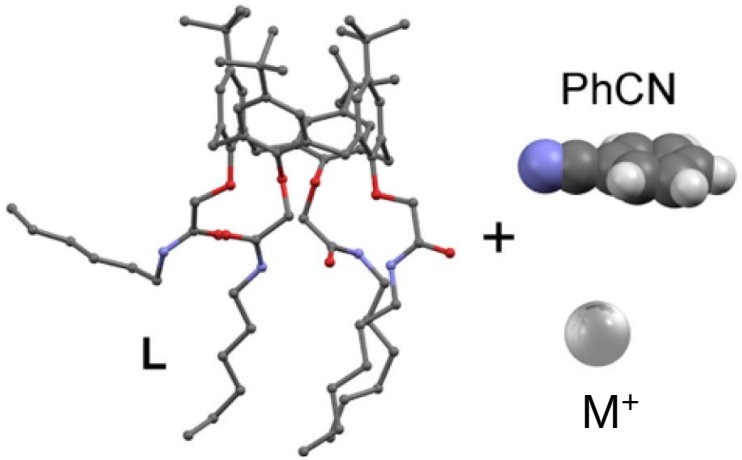
Interactions and structure

	Li^+		Na^+		K^+	
	$Li\mathbf{1}^+$	$Li\mathbf{1}MeCN^+$	$Na\mathbf{1}^+$	$Na\mathbf{1}MeCN^+$	$K\mathbf{1}^+$	$K\mathbf{1}MeCN^+$
$E(M^+–\mathbf{L})$ / kJ mol^{-1}	–492	–507	–	–431	–353	–360
$E(\mathbf{L}–MeCN)$ / kJ mol^{-1}	–505	–561	–	–578	–508	–594
$E(\mathbf{L}–MeCN_{inkl})$ / kJ mol^{-1}	–	–52	–	–51	–	–50
$E(M^+–MeCN)$ / kJ mol^{-1}	–18	–15	–	–6	–3	1
$E(M^+–MeCN_{inkl})$ / kJ mol^{-1}	–	8	–	8	–	7
t_{total} / ns		50		50		50
t / t_{ukupno}	0,009	0,991	0	1	0,001	0,999
N(carbonyl)	2,3	2,8	–	3,3	3,7	3,9
N(hydrogen bonds)	0,56	0,65	–	0,43	0,13	0,07
$N(MeCN_{inkl})$	–	6	–	1	–	4
$\bar{d}$ / Å	7,53 8,13	7,85 7,93	–	7,85 7,85	7,60 7,80	7,80 7,81
$\lvert d - d_{ref}\rvert$ / Å	0,41 0,46	0,22 0,23	–	0,21 0,21	0,38 0,45	0,20 0,21
$\sigma(d)$ / Å	0,42 0,50	0,28 0,28	–	0,26 0,26	0,48 0,51	0,25 0,25



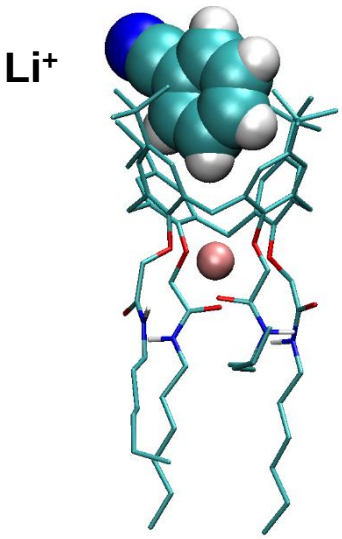


Calix[4]arene-cation complexes in benzonitrile

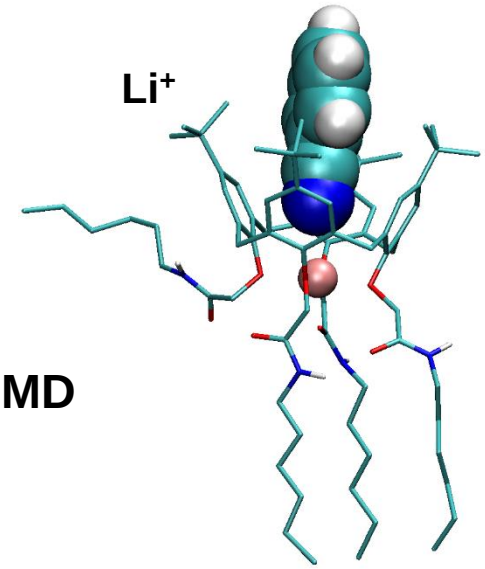


ITC

Kation	$\log\left(\frac{K}{\mathrm{dm^3 mol^{-1}}}\right) \pm \mathrm{SE}$	$\frac{\left(\Delta_r H^{\ominus} \pm \mathrm{SE}\right)}{\mathrm{kJ\ mol^{-1}}}$	$\frac{\left(\Delta_r S^{\ominus} \pm \mathrm{SE}\right)}{\mathrm{J\ K^{-1}\ mol^{-1}}}$
Li^+	6,17 ± 0,01	–8,9 ± 0,1	88,1 ± 0,4
Na^+	5,54 ± 0,01	–16,6 ± 0,1	50,4 ± 0,5
K^+	–[a]	–[a]	–[a]

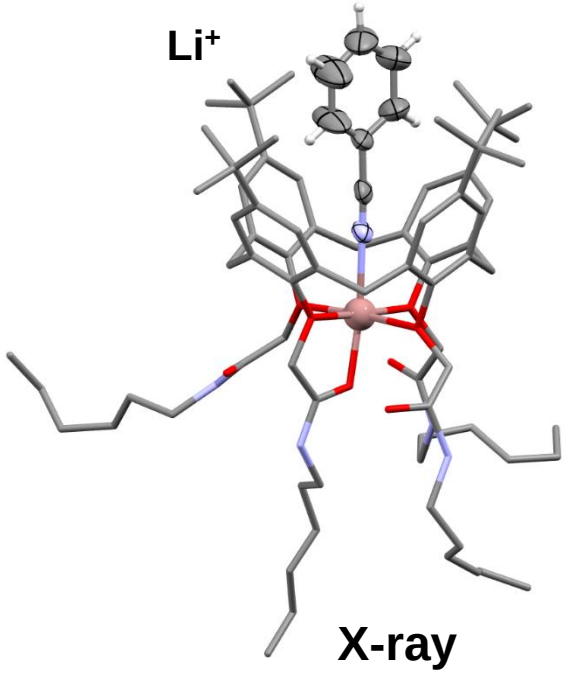


9 %



MD

64 %

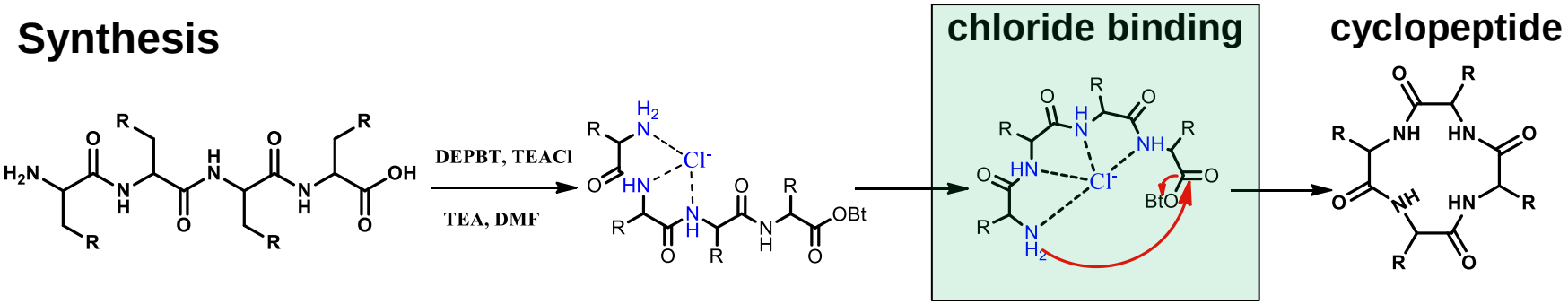


X-ray

G. Horvat, V. Stilinović, B. Kaitner, L. Frkanec, V. Tomišić, *Inorg. Chem.* **52** (2013) 12702–12712.

Cyclopeptide anion receptors

Synthesis

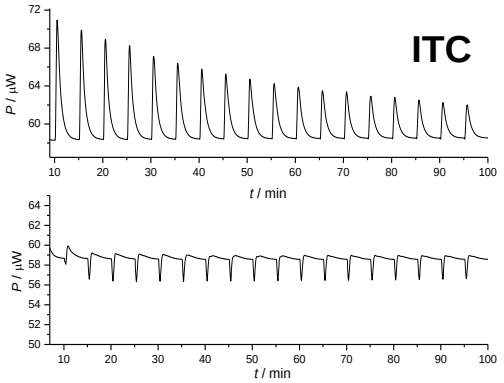


N. Vidović, G. Horvat, D. Riva, T. Rinkovec, N. Cindro, V. Tomišić, G. Speranza, *Org. Lett.* **2020**, *22*, 2129.

Cyclization yields

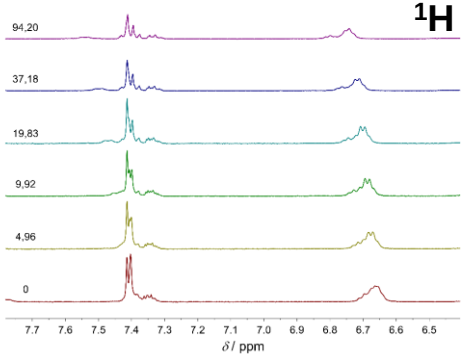
linear peptide[a]	Yield (%) LiCl/NaCl	NaTPB	TEACl	$NaClO_4$
K4 (1)	21[b]	8	47	0
K5 (2)	35[c]	26	43	0
K6 (3)	15[c]	10	17	0
L5 (7)		15	52	0
$(FLL)_2$ (8)	<5[c]	6	23	<5
I4 (11)	<5[b]	<5	18	0
I5 (12)	11[c]	<5	26	0
S5 (13)	21[c]		29	
F5 (14)			46	

ITC

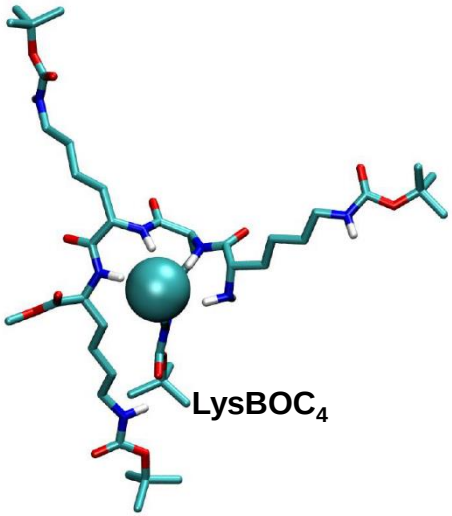


log *K* around 1.5

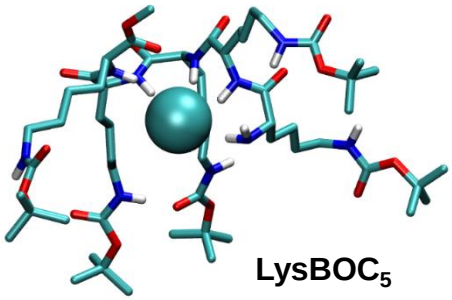
^{1}H NMR



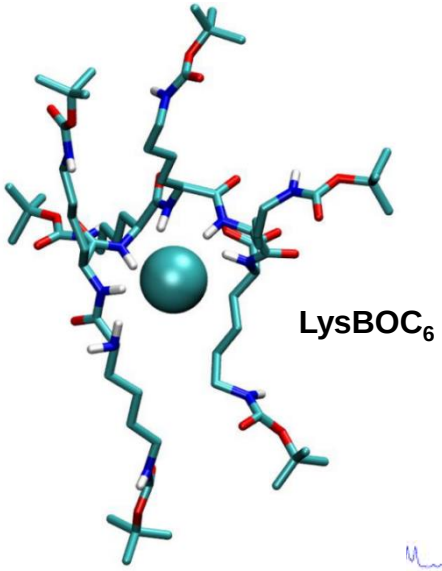
Structures of chloride-linear peptide complexes



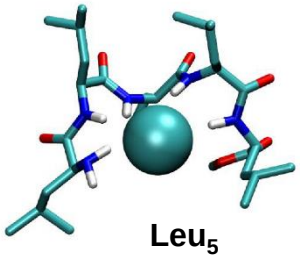
$LysBOC_4$



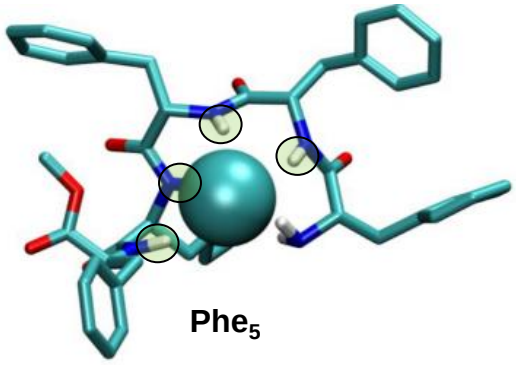
$LysBOC_5$



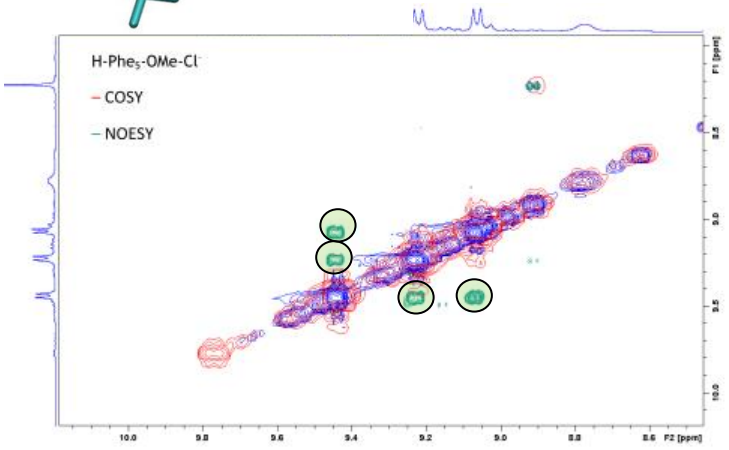
$LysBOC_6$



Leu_5



Phe_5

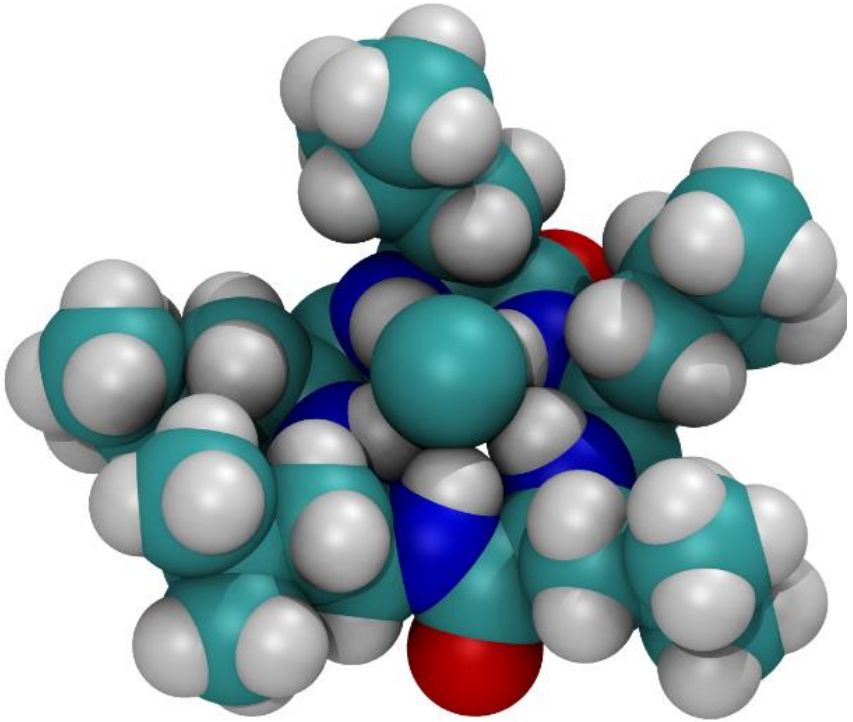


RESEARCH HIGHLIGHTS

Nature Reviews Chemistry | https://doi.org/10.1038/s41570-020-0185-0 | Published online 15 April 2020

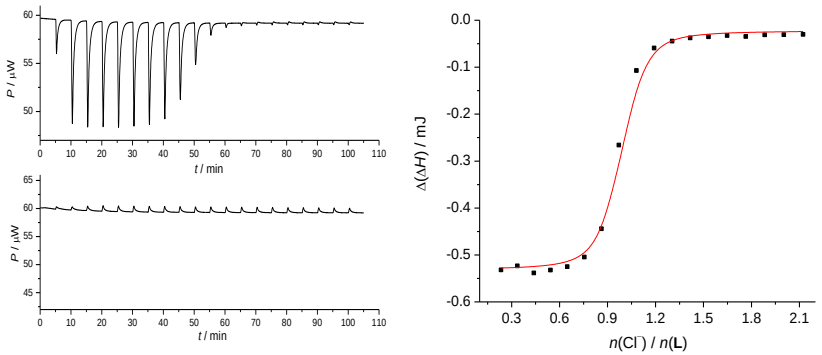
Running rings around chloride

Thermodynamic and MD studies of anion complexation by cyclopentaleucine in MeCN and DMSO



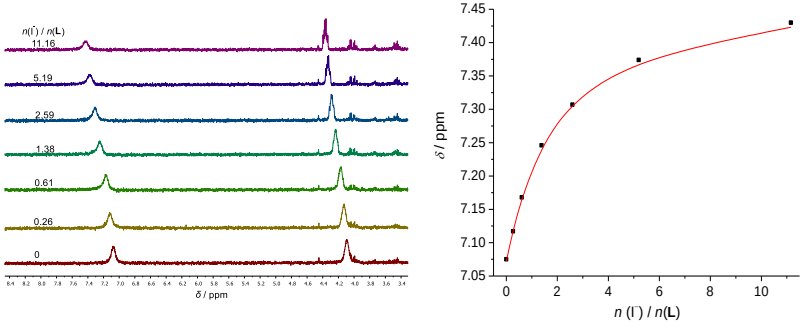
MD simulations

ITC



Leu_5 titration with Cl^- in MeCN

^{1}H NMR



Leu_5 titration with I^- in MeCN

G. Horvat, S. Tarana, N. Vidović, N. Cindro, G. Speranza, V. Tomišić, *J. Mol. Liq.* **2021**, *340,* 116848.

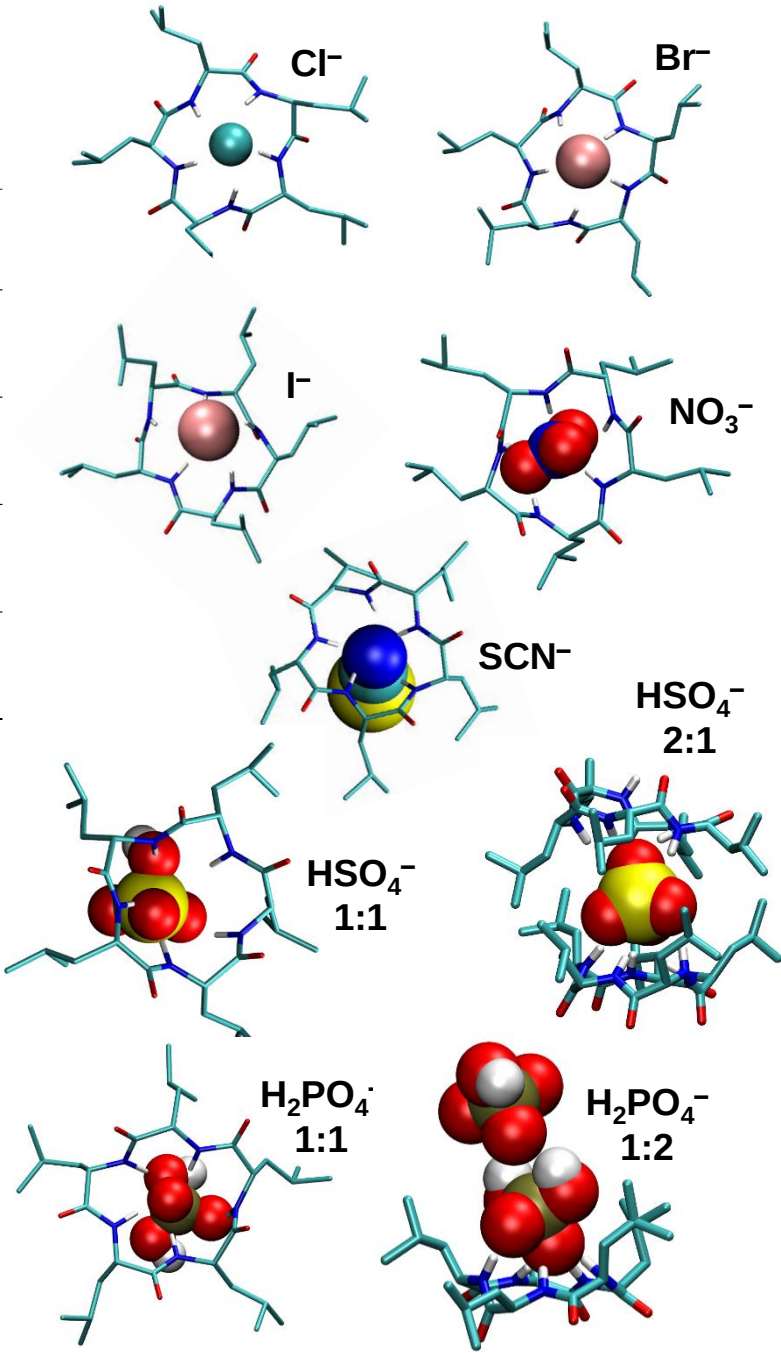
Cyclopeptide-anion complexation in MeCN

1:1 complexes

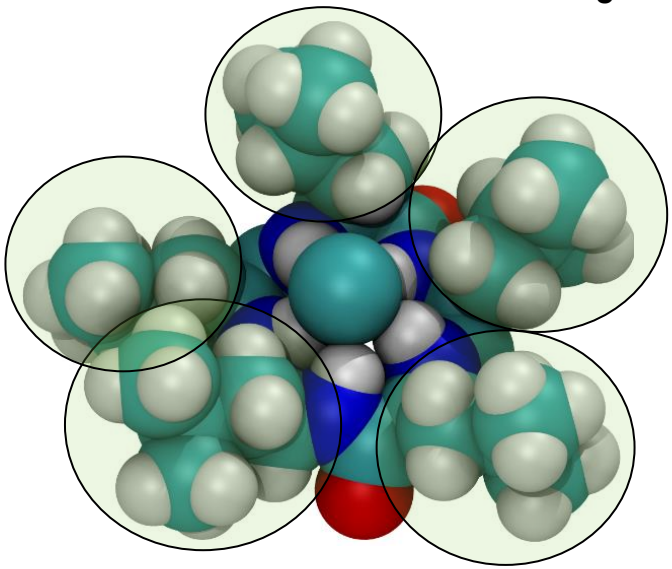
Anion	$\log\left(\frac{K}{\mathrm{dm^3 mol^{-1}}}\right) \pm \mathrm{SE}$	$\frac{(\Delta_r G^\circ \pm \mathrm{SE})}{\mathrm{kJ\ mol^{-1}}}$	$\frac{(\Delta_r H^\circ \pm \mathrm{SE})}{\mathrm{kJ\ mol^{-1}}}$	$\frac{(\Delta_r S^\circ \pm \mathrm{SE})}{\mathrm{J\ mol^{-1}\ K^{-1}}}$
Cl^-	5.84 ± 0.03[a]	–33.33 ± 0.11	–10.68 ± 0.08	75.9 ± 0.6
Br^-	4.70 ± 0.01[a]	–26.82 ± 0.06	–4.84 ± 0.02	73.7 ± 0.2
I^-	3.20 ± 0.03[a] 3.12[b]	–18.27 ± 0.15	1.91 ± 0.08	67.7 ± 0.3
SCN^-	2.90 ± 0.02[a] 2.77[b]	–16.5 ± 0.1	–4.72 ± 0.095	39.7 ± 0.7
NO_3^-	3.18 ± 0.01[a] 3.29[b]	–18.16 ± 0.04	–6.08 ± 0.04	40.5 ± 0.3

Complexes of higher stoichiometry

Anion	$\log\left(\frac{K}{\mathrm{dm^3 mol^{-1}}}\right) \pm \mathrm{SE}$	$\frac{(\Delta_r G^\circ \pm \mathrm{SE})}{\mathrm{kJ\ mol^{-1}}}$	$\frac{(\Delta_r H^\circ \pm \mathrm{SE})}{\mathrm{kJ\ mol^{-1}}}$	$\frac{(\Delta_r S^\circ \pm \mathrm{SE})}{\mathrm{J\ mol^{-1}\ K^{-1}}}$
HSO_4^-	4.38 ± 0.02 (1:1) 2.96 ± 0.05 (2:1)	–25.0 ± 0.1 –16.9 ± 0.3	–16.0 ± 0.1 0.4 ± 0.3	30.2 ± 0.7 58 ± 2
$H_2PO_4^-$	4.56 ± 0.02 (1:1) 4.18 ± 0.02 (1:2)	–26.0 ± 0.1 –23.8 ± 0.1	–12.6 ± 0.3 –79.7 ± 0.6	45 ± 1 –187 ± 2



Structures of anion-Leu_5 complexes

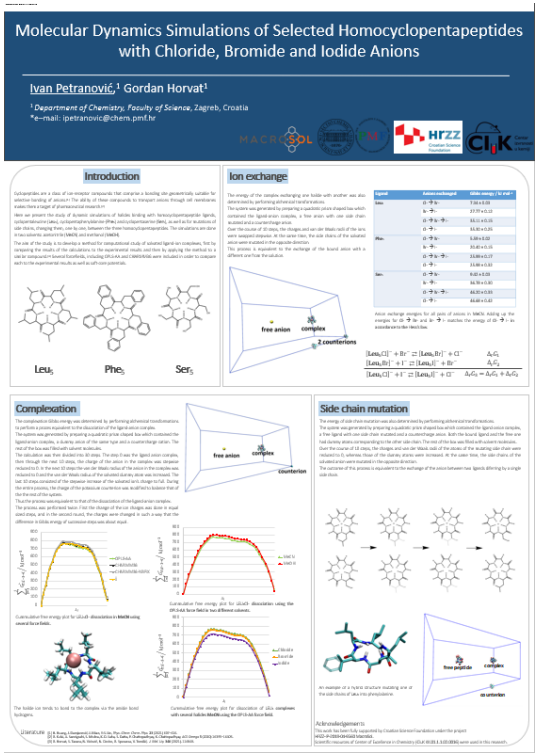


***endo* complexes**

Average number of coordinated amide protons in MeCN

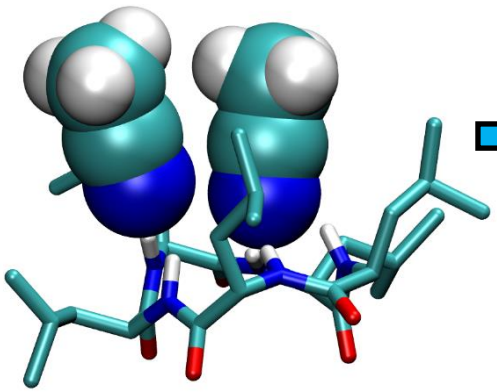
anion	Cl^-	Br^-	I^-	NO_3^-	SCN^-	HSO_4^-	$H_2PO_4^-$
N(–H)	4.98	4.98	4.88	4.95	4.77	4.75	4.97

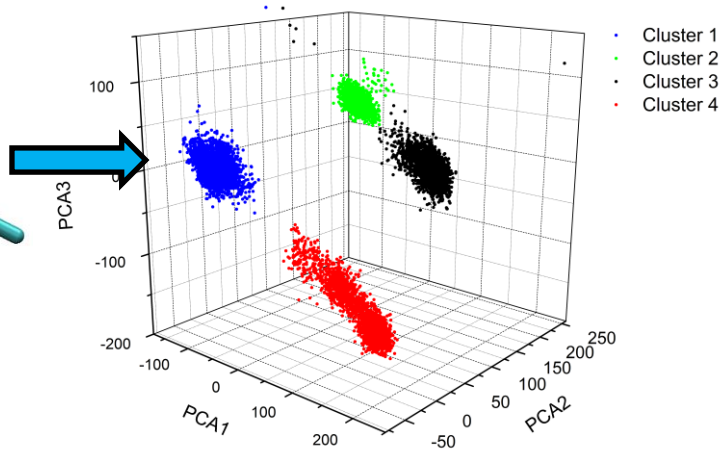
Free energy calculations by MD



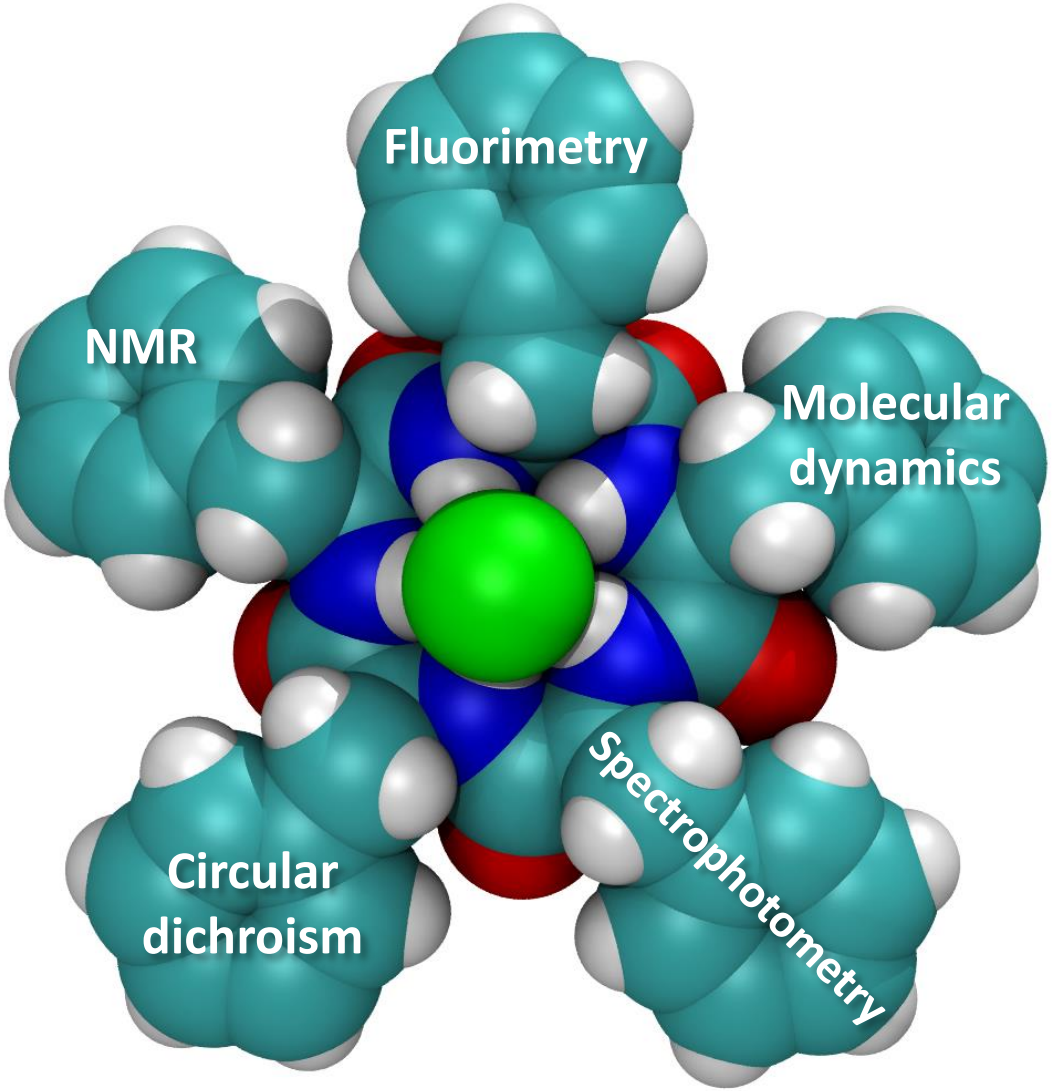
CCD2023 poster: Ivan Petranović

Structure of free Leu_5 in MeCN



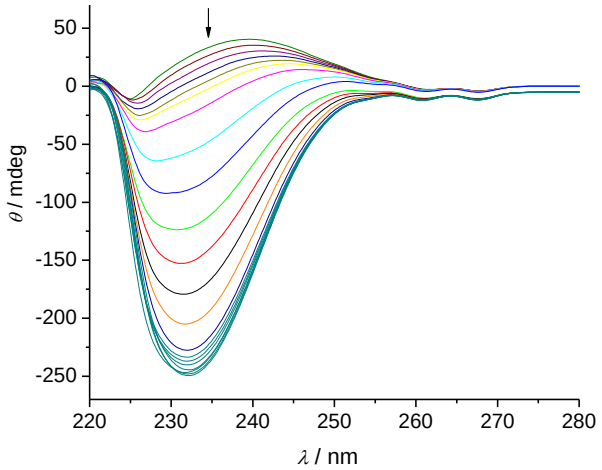


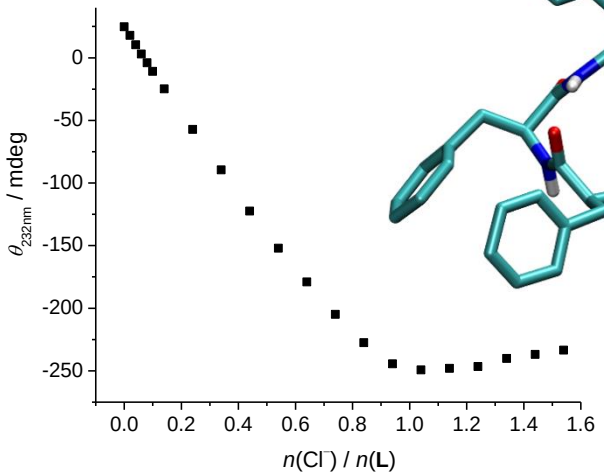
Anion-Sensing Properties of Cyclopentaphenylalanine

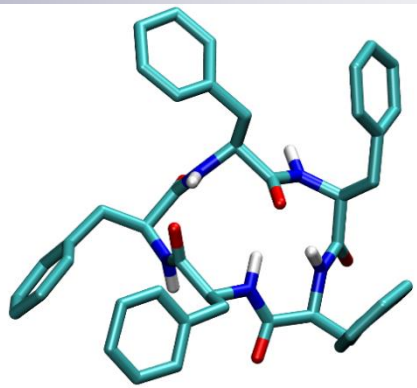


I. Petters, M. Modrušan, N. Vidović, I. Crnolatac, N. Cindro, I. Piantanida, G. Speranza, G. Horvat, V. Tomišić, *Molecules* **2022**, *27,* 3918.

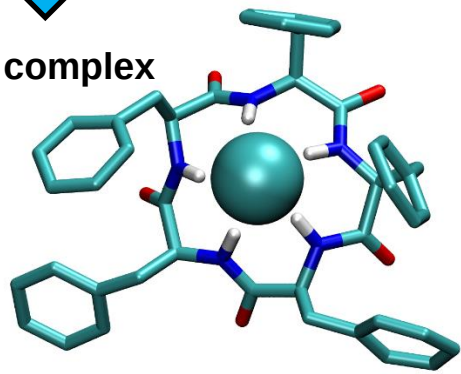
Circular dichroism titrations in MeCN





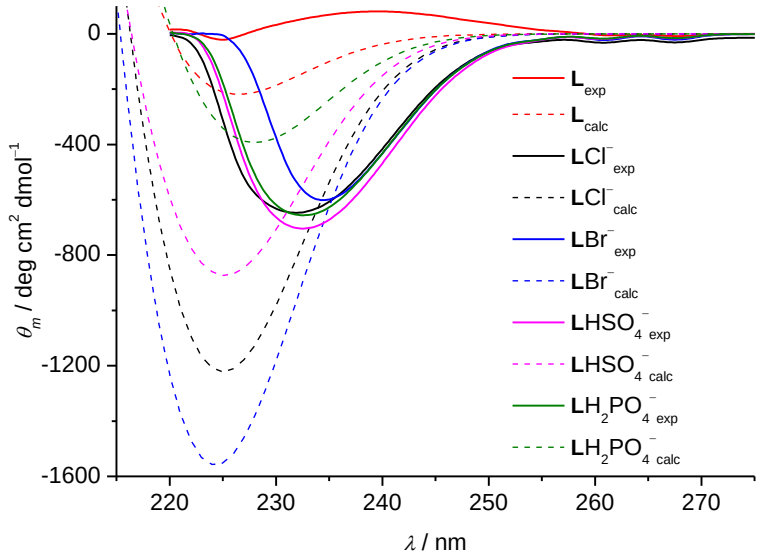


free



complex

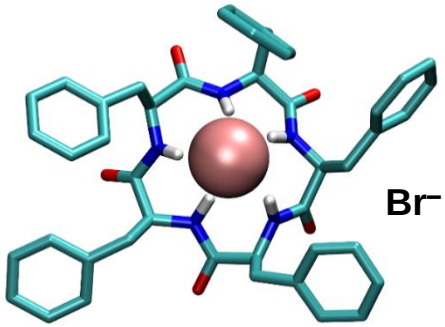
Phe_5 titration with Cl^- in MeCN



Experimental vs calculated CD spectra

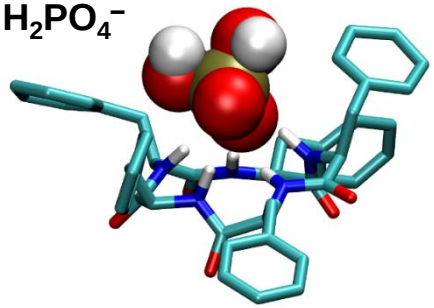
↓

Dichrocalc webserver + our MD data

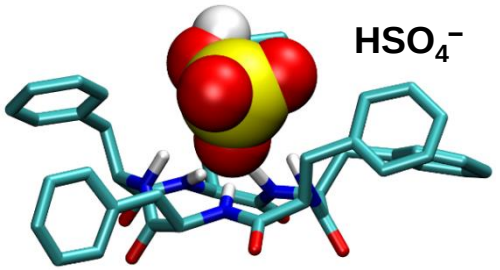


Br^-

$H_2PO_4^-$



HSO_4^-



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