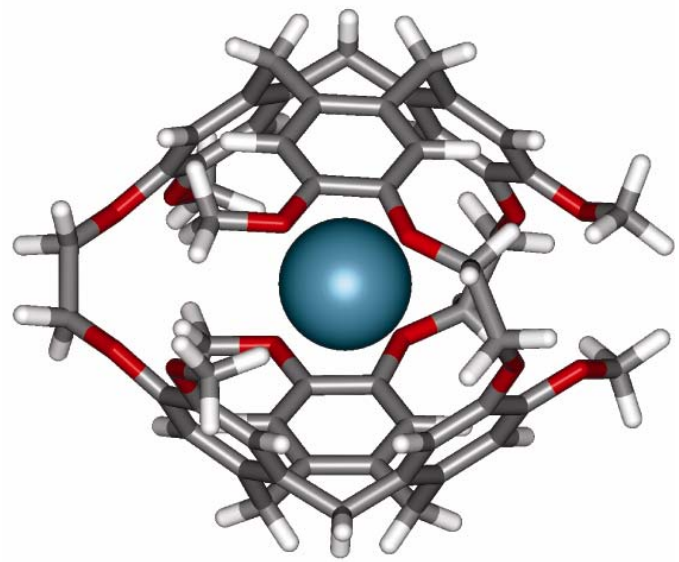
Xe in cryptophane cages

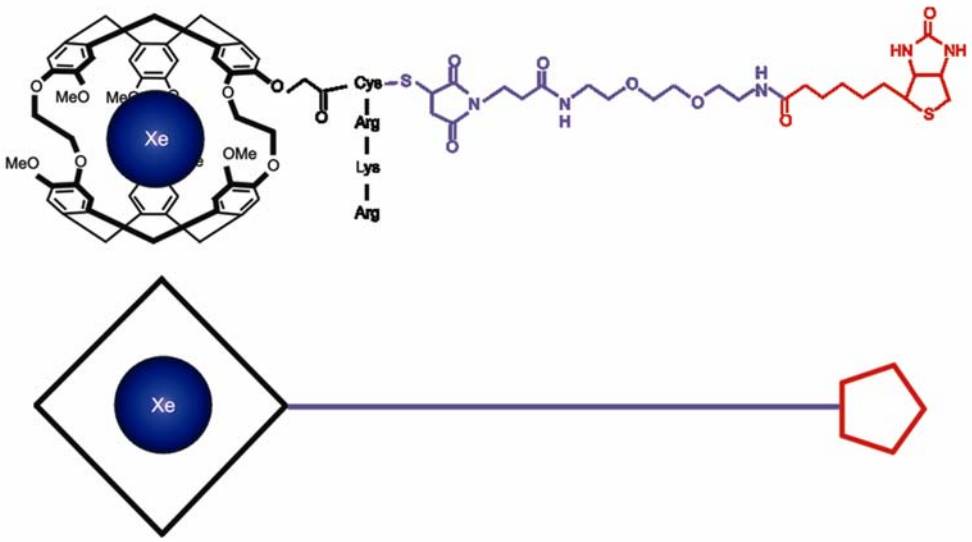


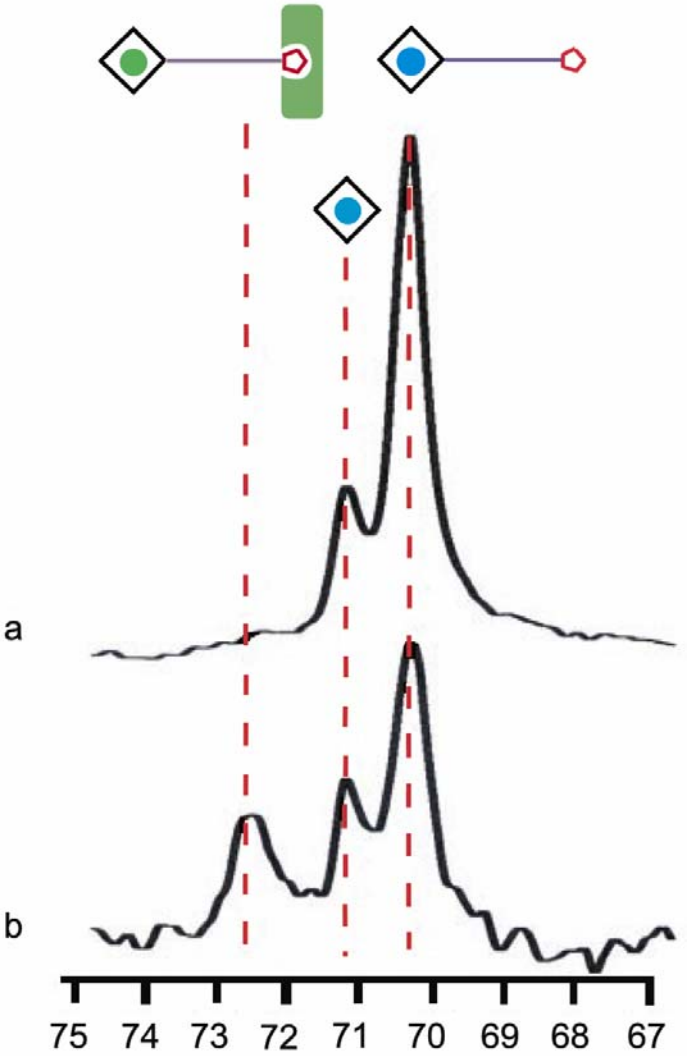
Devin N. Sears
Cynthia J. Jameson

University of Illinois at Chicago

XeMAT 2003
May 27-31, 2003
La Colle sur Loup, FRANCE

MOTIVATION Xe as biosensor (Pines, Wemmer et al., 2001)



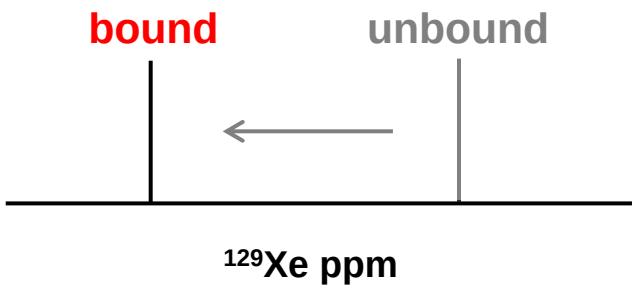


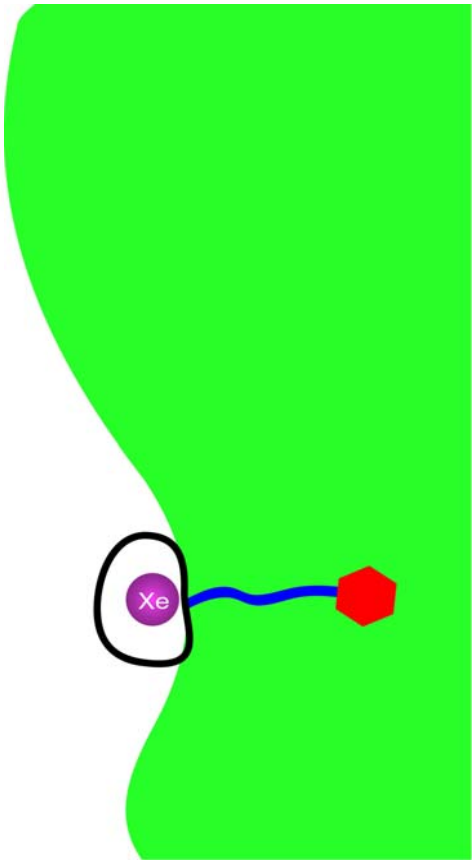
- Experiments on Xe in **cryptophane cages** provide **model systems** for comparison
- Unique cages A, 223, 332, and E
- Temperature dependence of Xe @cryptoA
- Xe isotope shifts upon deuteration of cage

M.M. Spence, S.M. Rubin, I.E. Dimitrov, E.J. Ruiz, D.E. Wemmer, A. Pines, S.Q. Yao, F. Tian, and P.G. Schultz Proc. Nat. Acad. Sci. **2001**, 98, 10654-10657.

Xe as a biosensor

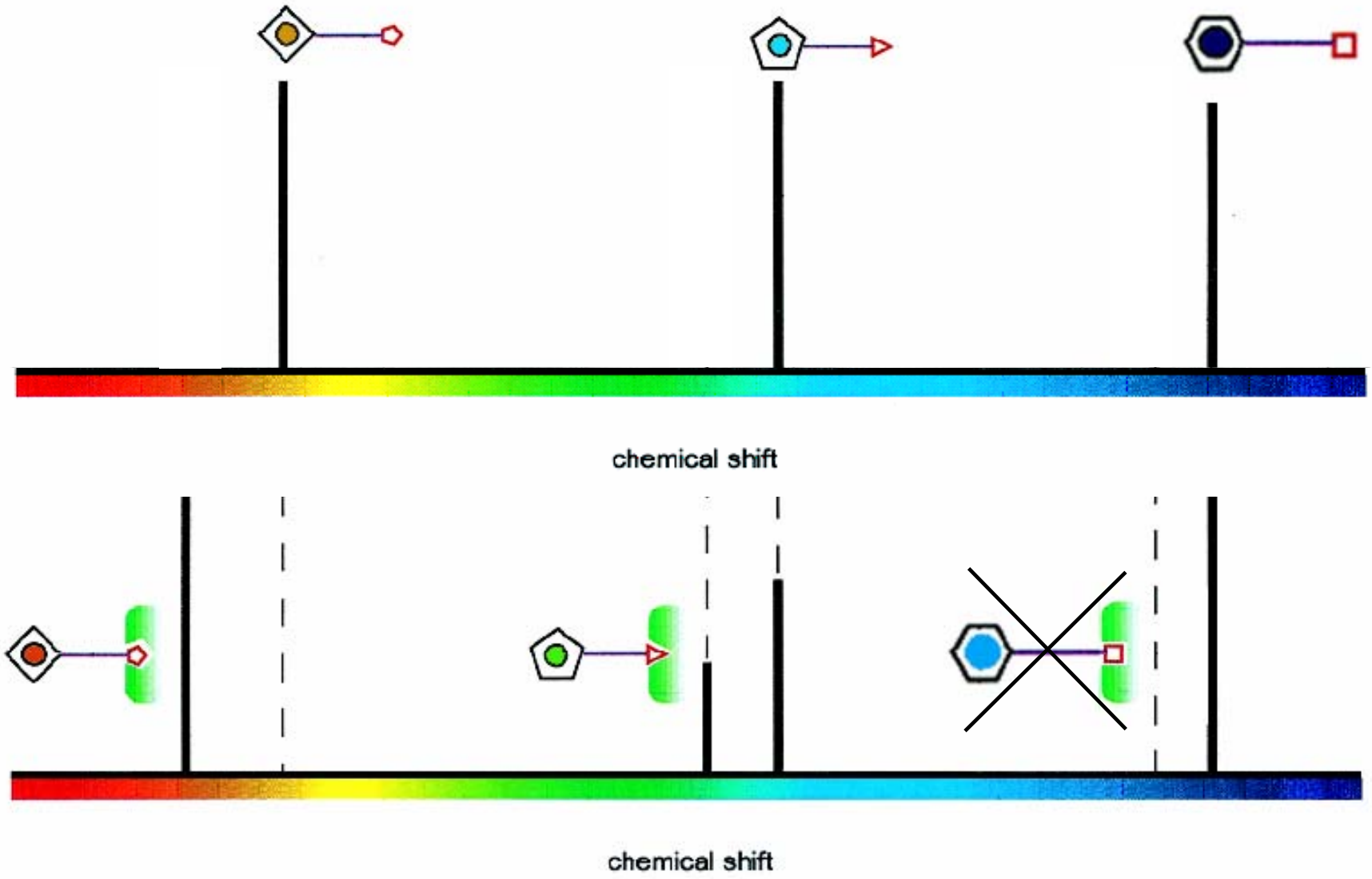
(Pines, Wemmer, et al. 2001)





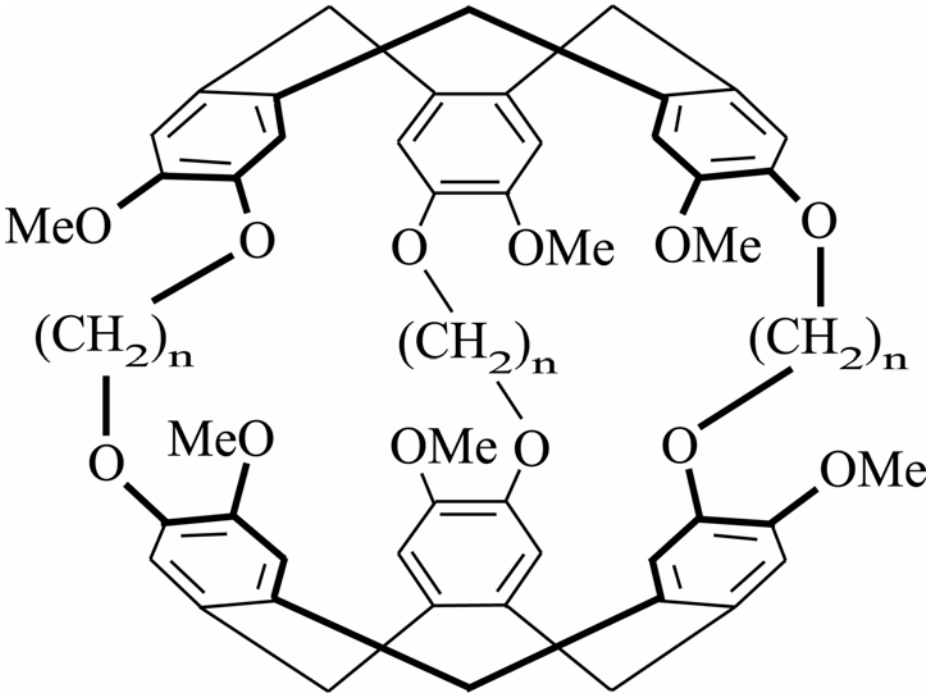
This slide courtesy of E. Janette Ruiz

Multiplexing



The cryptophanes

- Two cyclotriveratrylene bowls
- Connected by aliphatic linker $(CH_2)_n$
- n=2 Cryptophane-A (cryptoA)
- n=3 Cryptophane-E (cryptoE)
- n=2,2,3 Cryptophane-223
- n=2,3,3 Cryptophane-233



To calculate average Xe chemical shifts we need:

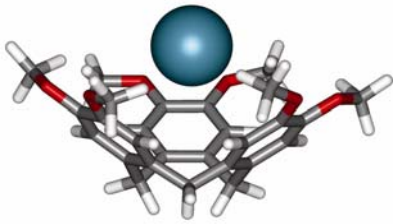
- Solution structures of cryptophanes-A, -223, -233, and -E
- Suitable fragment for *ab initio* calculations of xenon shielding surface
- Reasonable set of potential functions

X-Ray crystal structure cryptoA*

Average structural parameters of 1/3 cyclotriveratrylene

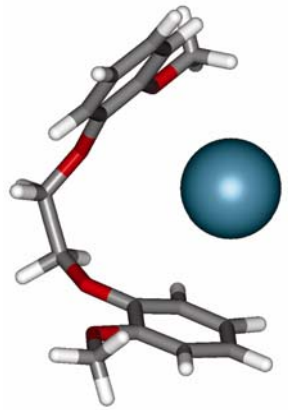
Symmetrize with GAMESS to obtain bowl structure

Optimize orientation of methoxy groups (HF & B3LYP) with Xe atom at center of bowl



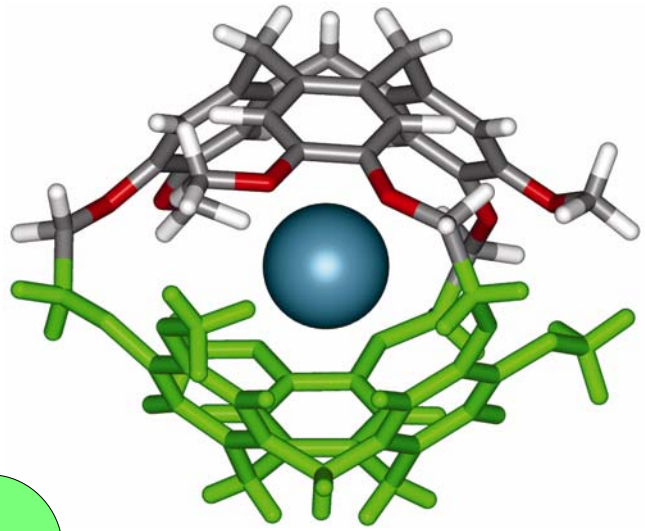
Use two bowls to form cage

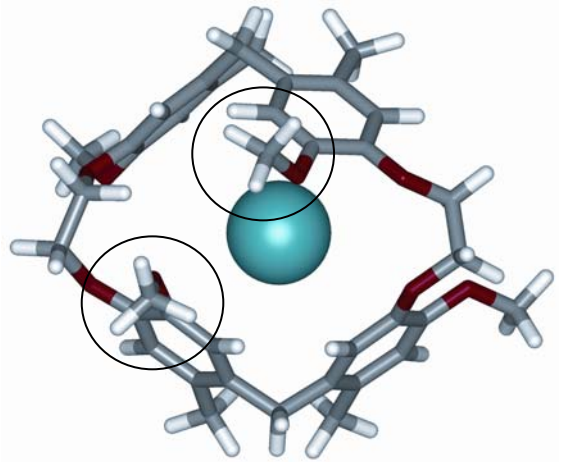
Geometry optimization of molecular fragment with Xe atom in center position
Constrain all coordinates except
$-O-CH_2-CH_2-O-$



Shielding surface calculations

Geometry optimization of molecular fragment with Xe atom in center position
Constrain all coordinates except methoxy CH_3 groups



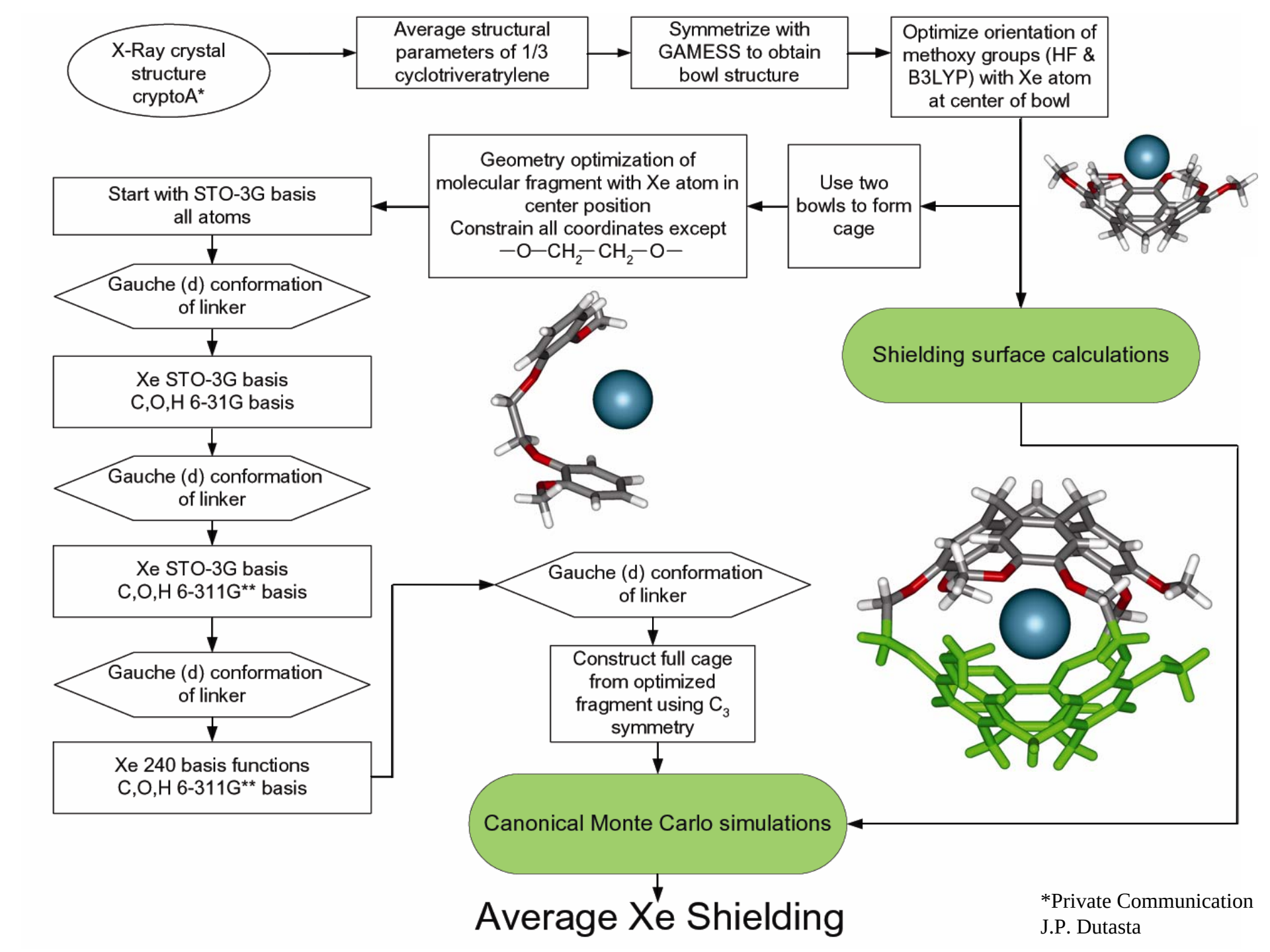


Construct full cage from optimized fragment using C_3 symmetry

Canonical Monte Carlo simulations

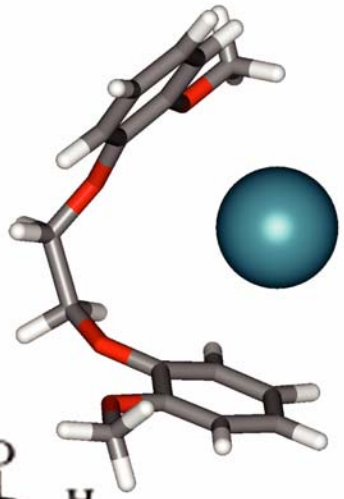
Average Xe Shielding

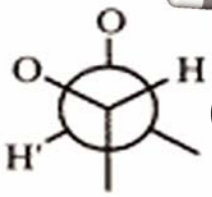
*Private Communications
J. P. Dutasta



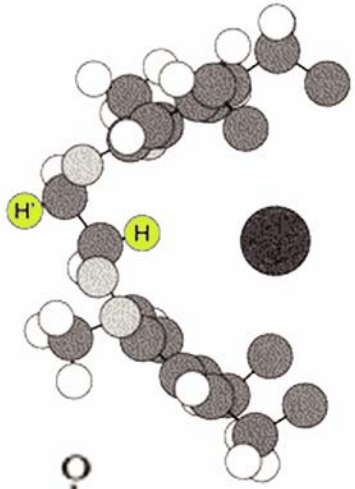
*Private Communication
J.P. Dutasta

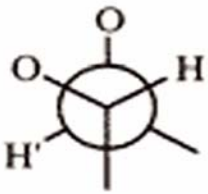
The average structure of Xe@cryptoA to be used for Monte Carlo simulations





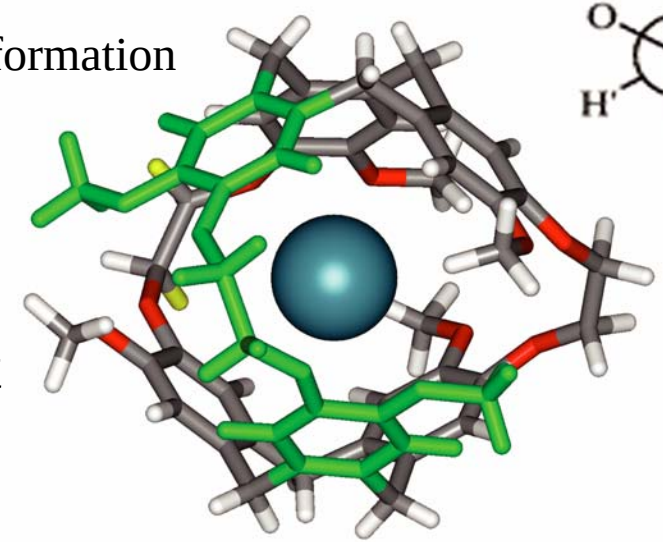
(d) conformation





(d) conformation

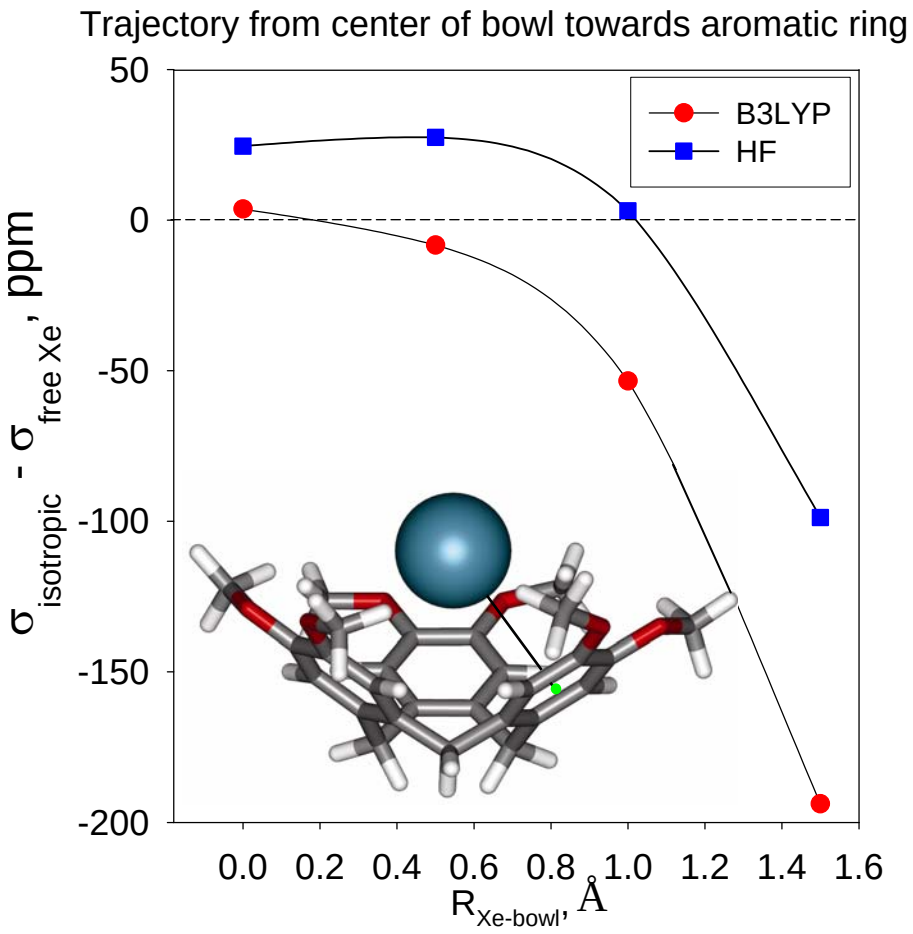
Pines et al. 1999*

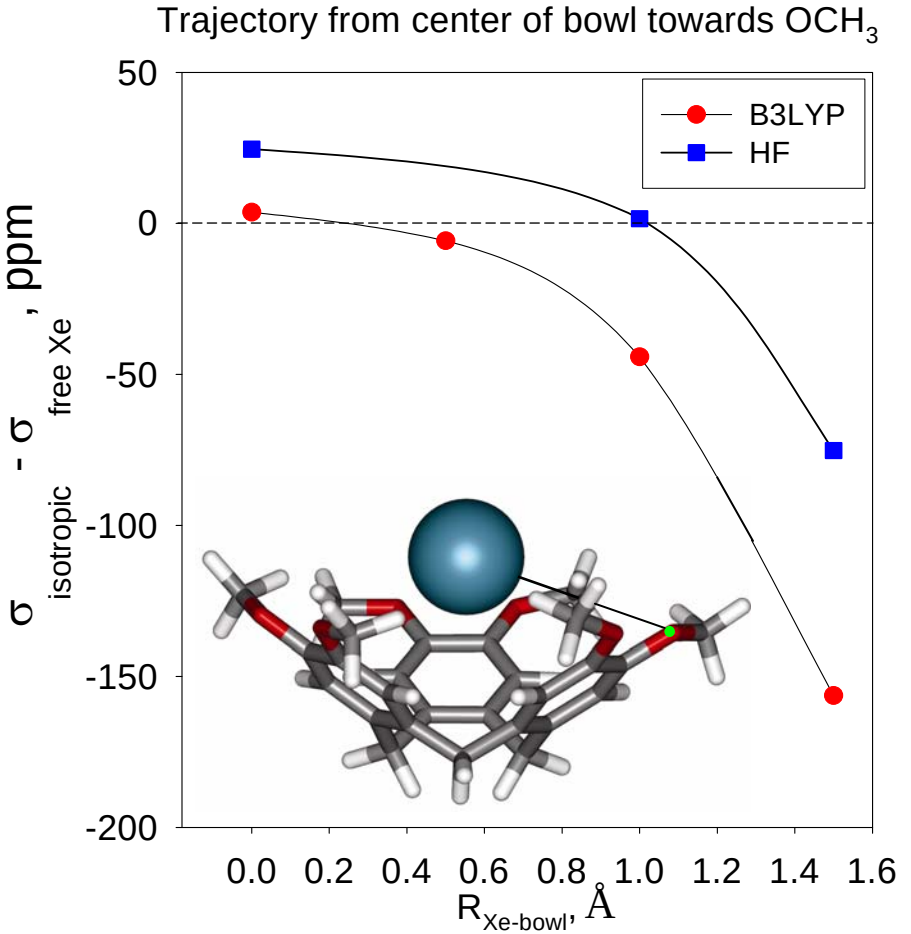


Minimum energy structure arrived at is completely consistent with SPINOE experiments by Pines et al!

* M., Luhmer, B. M. Goodson, Y. Q. Song, D. D. Laws, L. Kaiser, M. C. Cyrier, and A. Pines J. Am. Chem. Soc. **1999**, 121, 3503.

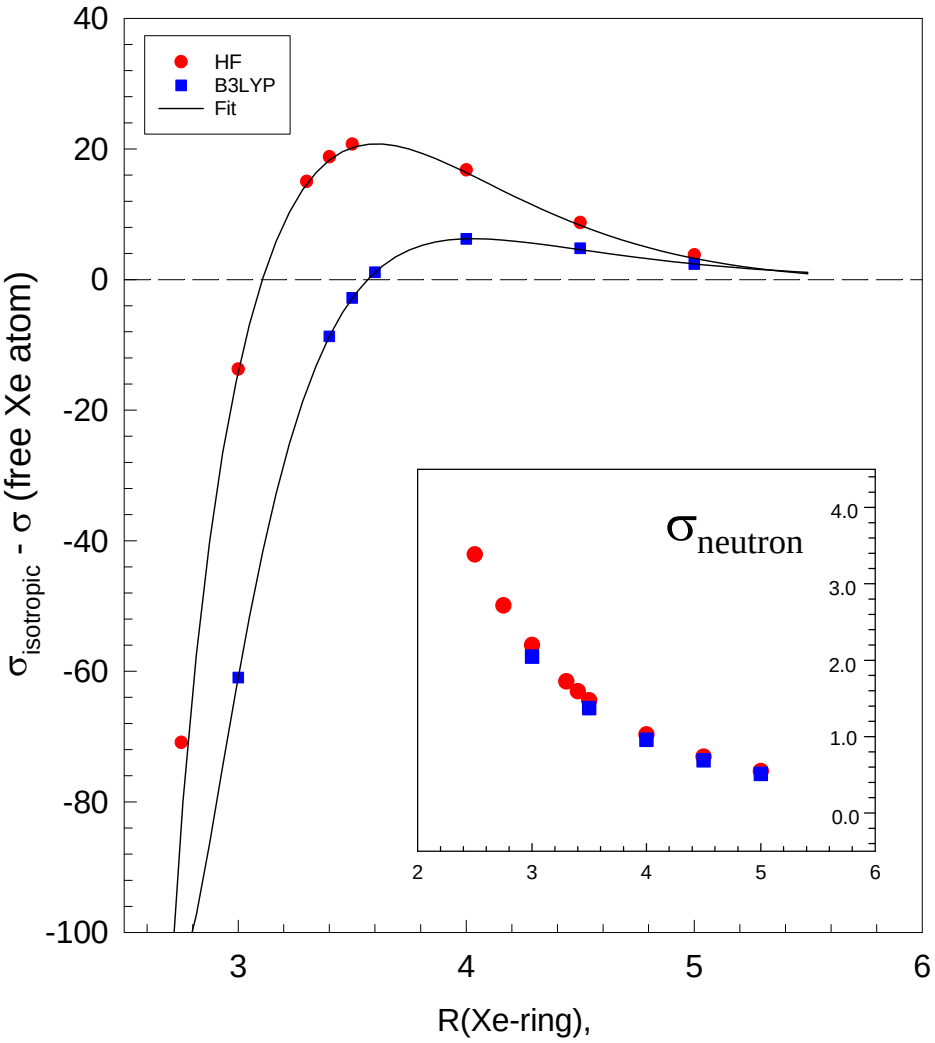
σ(Xe): DFT vs. Hartree-Fock



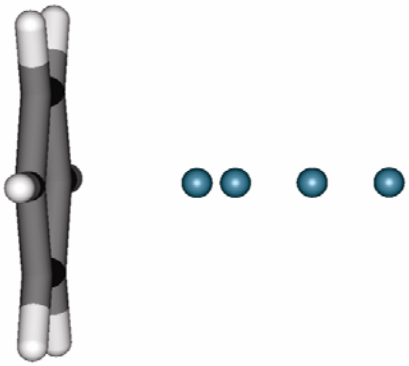


- Electron correlation is necessary to properly describe xenon shielding response to electronic environment of the bowl.
- For many Xe locations, Hartree-Fock leads to Xe that is shielded compared to free atom, contrary to experiment!

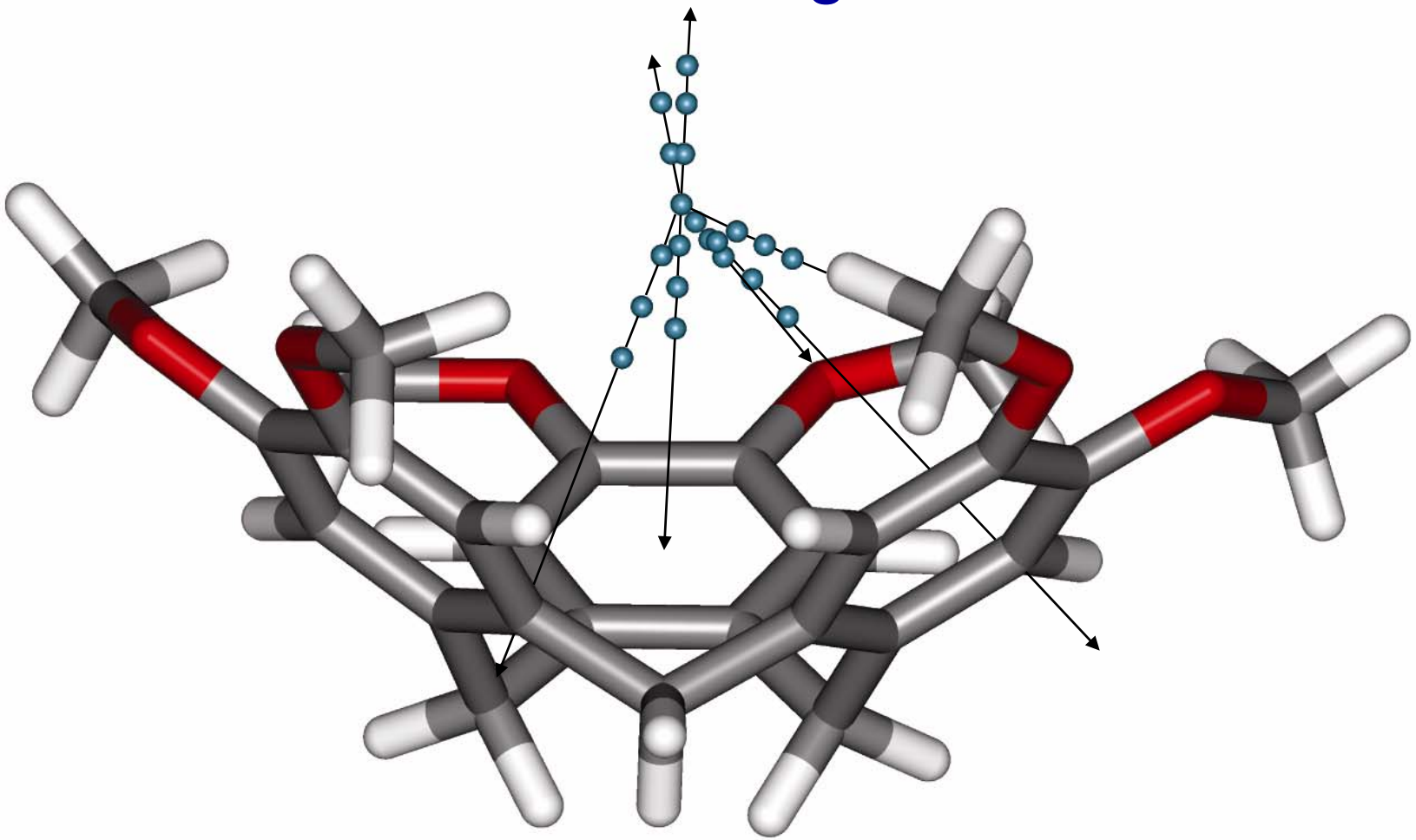
Xe interacting with aromatic systems



- Electron correlation is necessary to properly describe Xe@benzene
- Ring currents (probed by neutron) do not fully account for the Xe shielding response
- Even with electron correlation a small positive shielding is found at intermediate distances

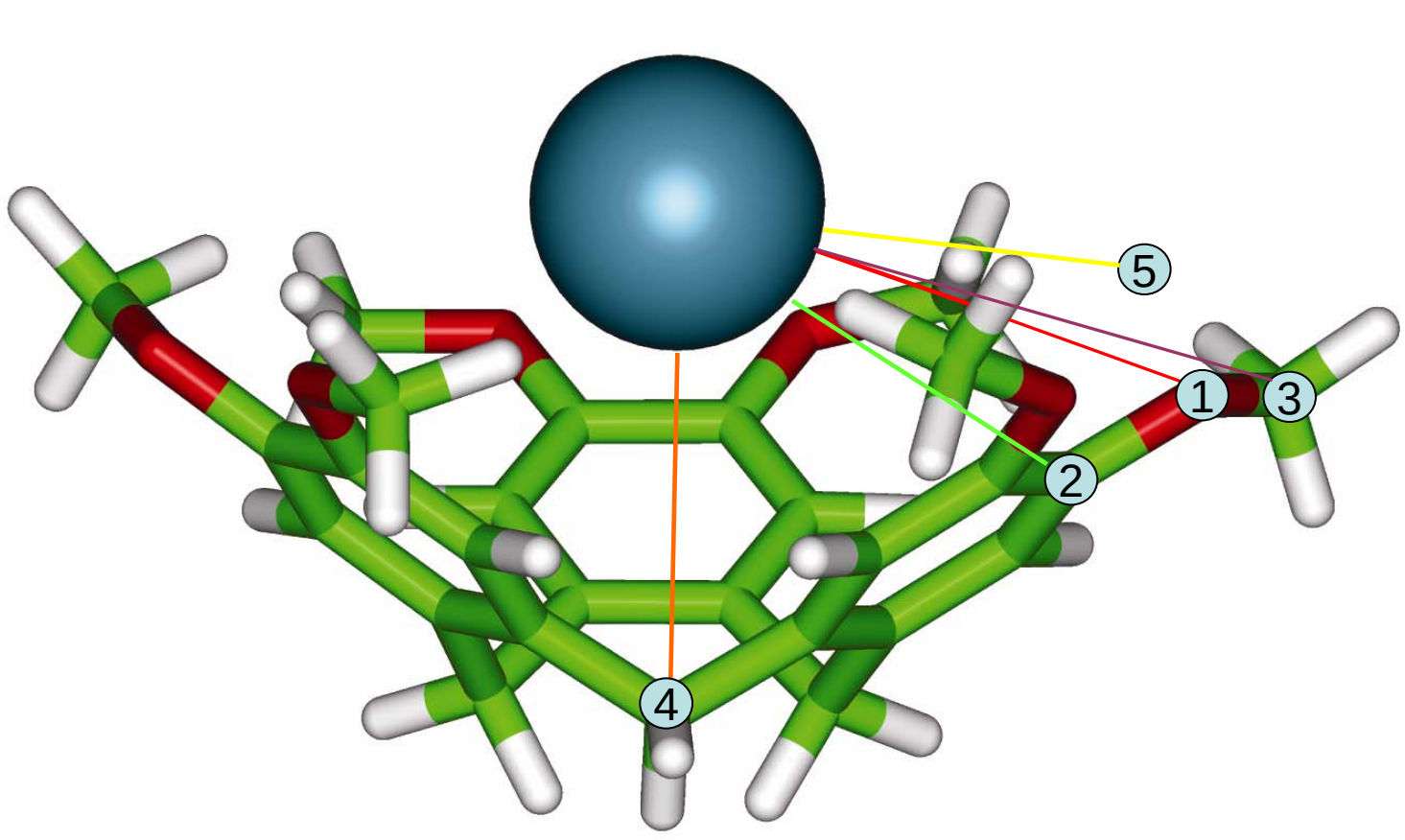


Xe shielding surface calculations in the model fragment



- Single cyclotriveratrylene
- Hartree-Fock and DFT (B3LYP)
- 6-311G** basis set on C, O, and H atoms
- 240 basis functions on Xe atom

5-site representation of the shielding surface



Representation of ab initio values by site-site shielding functions

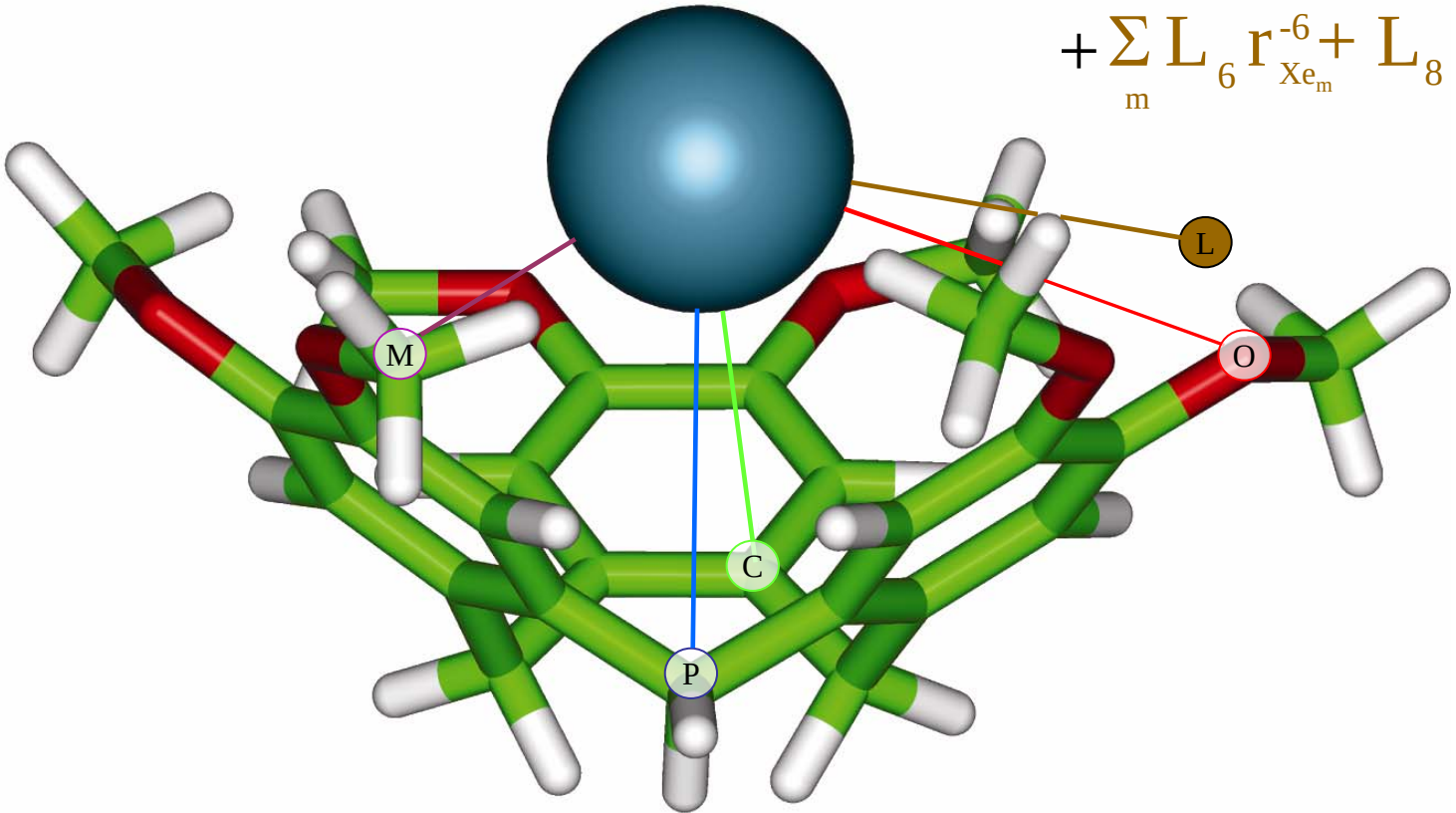
Ab initio points fit to the following site-site functional form:

$$[\sigma_{isotropic}(Xe) - \sigma(\text{free Xe})] =$$

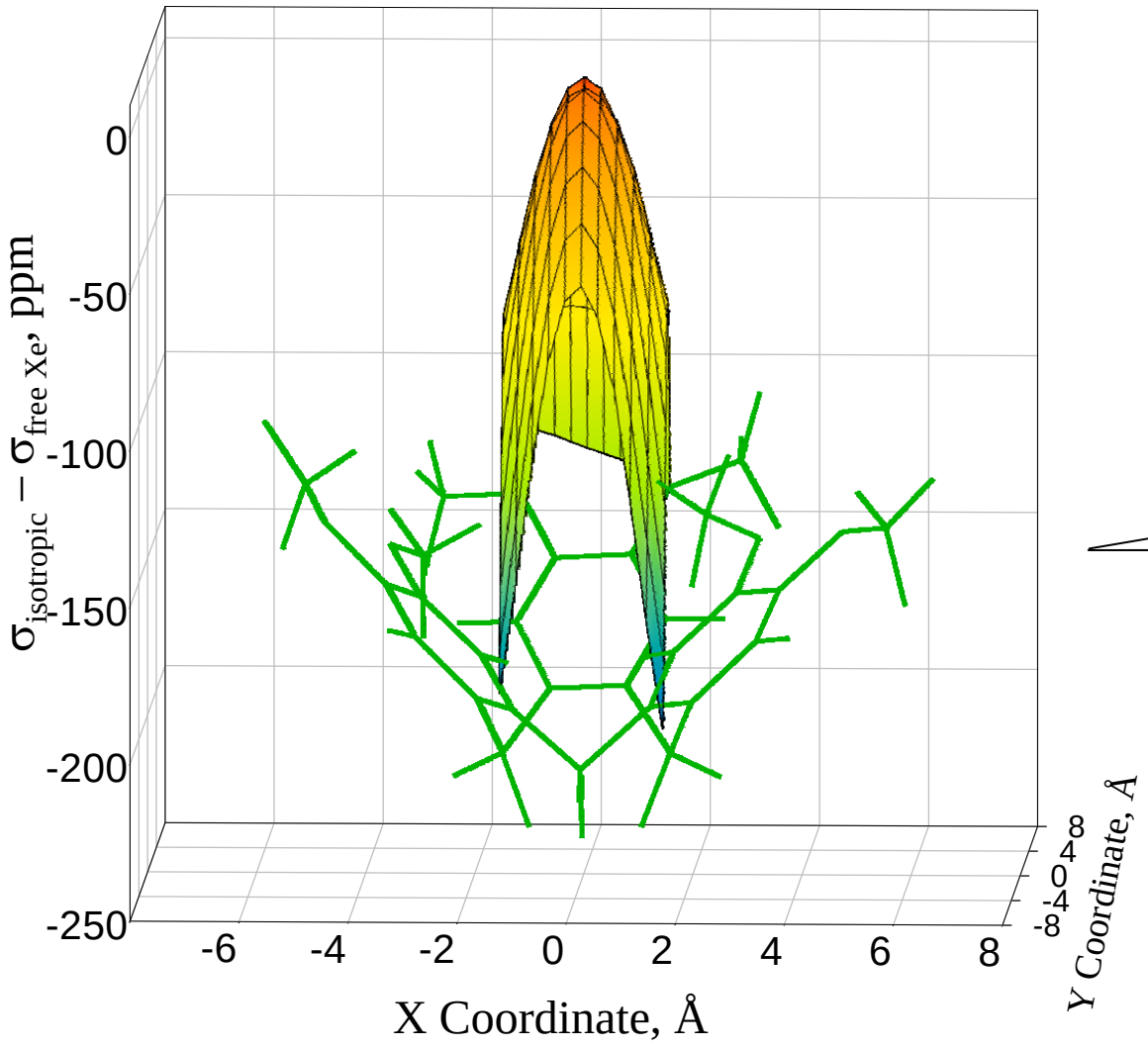
$$\sum_i O_6\, r_{Xe_i}^{-6} + O_8\, r_{Xe_i}^{-8} + O_{10}\, r_{Xe_i}^{-10} + \sum_j C_6\, r_{Xe_j}^{-6} + C_8\, r_{Xe_j}^{-8} + C_{10}\, r_{Xe_j}^{-10}$$

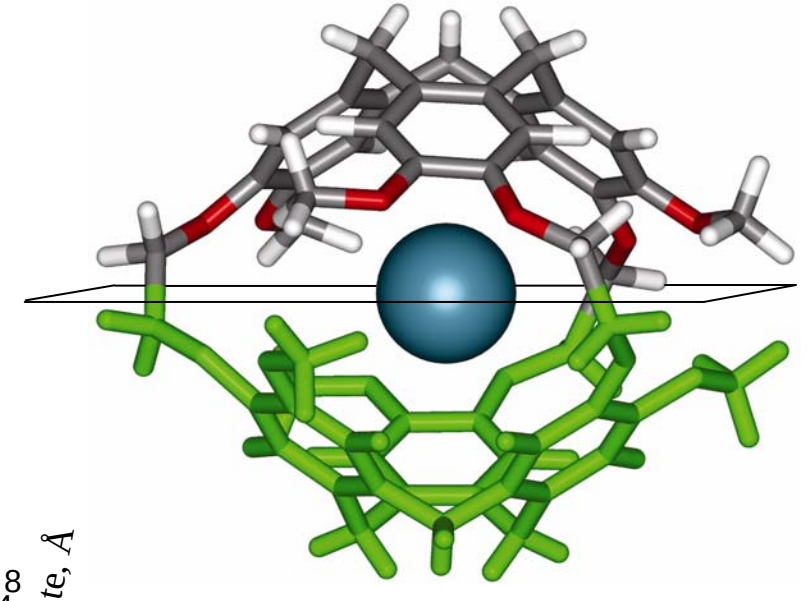
$$+ \sum_k M_6 r_{Xe_k}^{-6} + M_8 r_{Xe_k}^{-8} + M_{10}\, r_{Xe_k}^{-10} + \sum_n P_6\, r_{Xe_n}^{-6} + P_8\, r_{Xe_n}^{-8} + P_{10}\, r_{Xe_n}^{-10}$$

$$+ \sum_m L_6\, r_{Xe_m}^{-6} + L_8\, r_{Xe_m}^{-8} + L_{10}\, r_{Xe_m}^{-10}$$



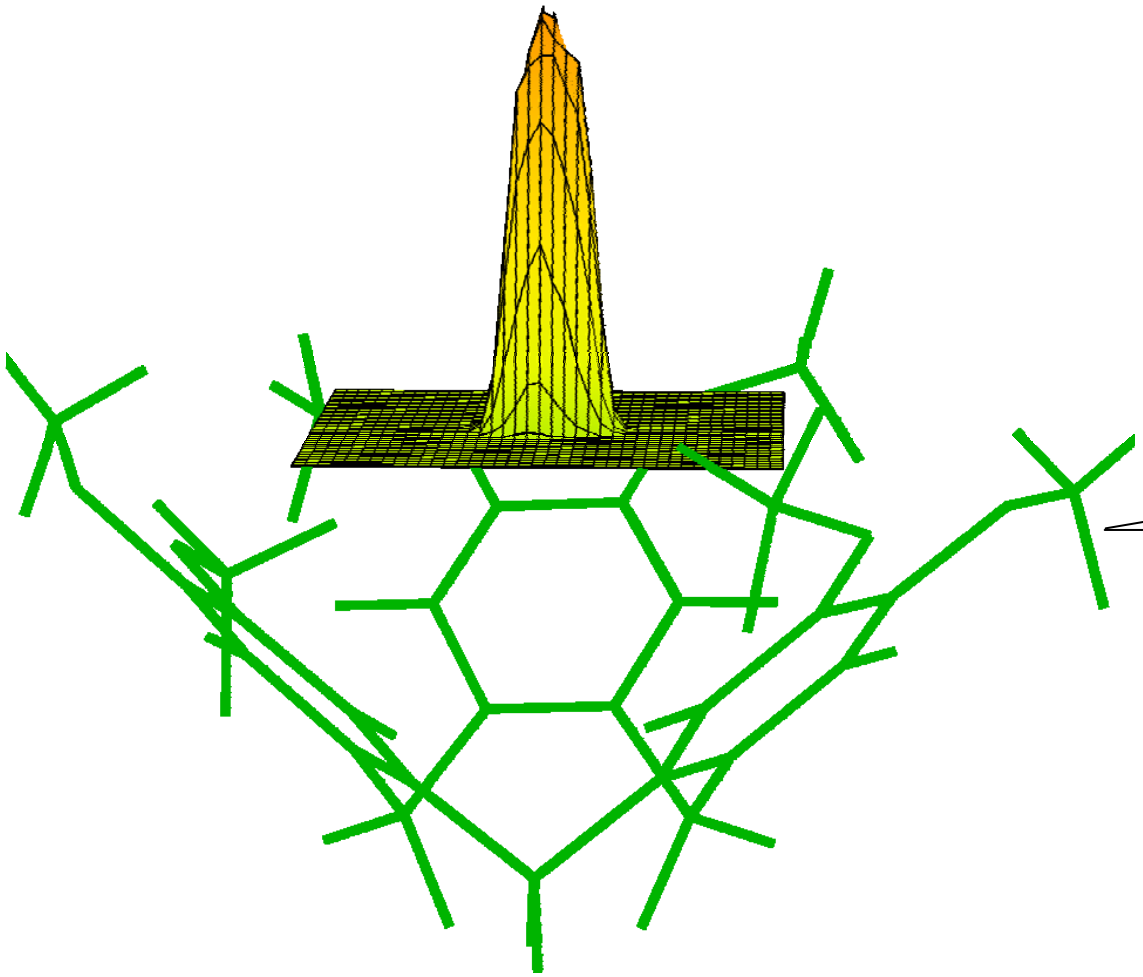
The Xe shielding surface for Xe@cryptoA

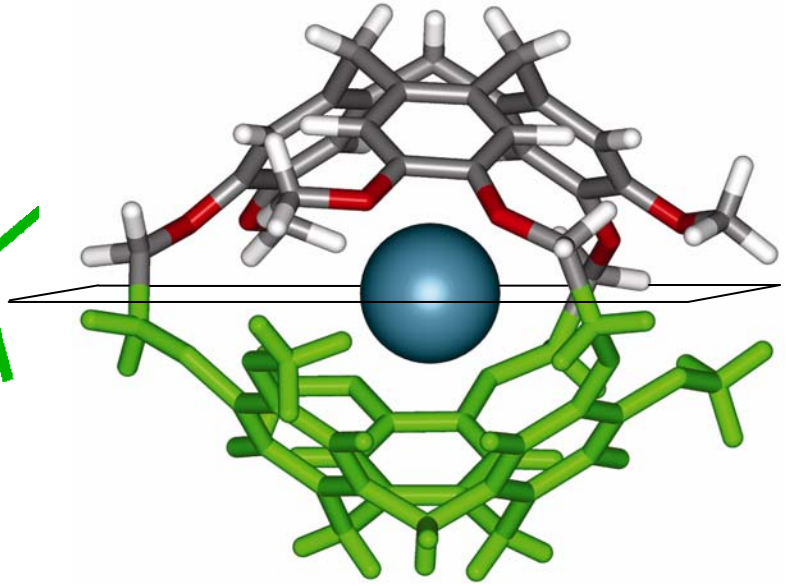




One-body distribution function for Xe@cryptoA

from Monte Carlo simulations

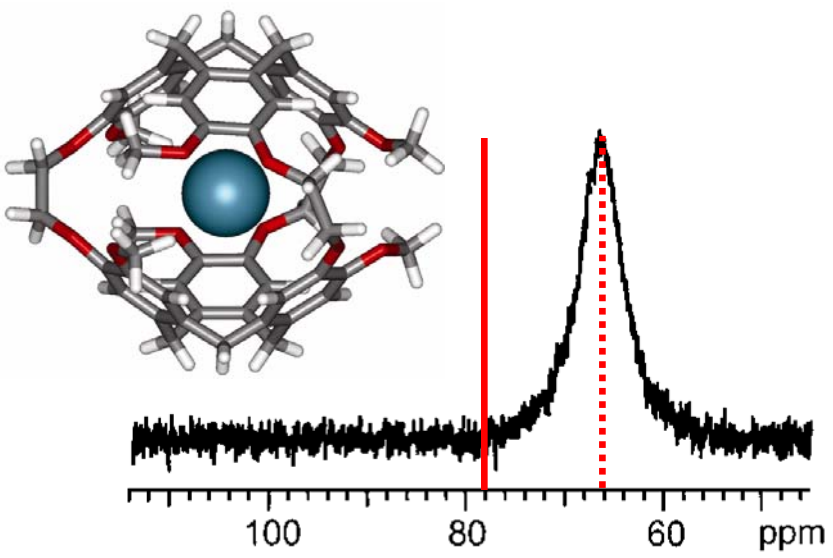




Monte Carlo average shielding for Xe@cryptoA

δ(ppm) relative to free Xe atom

***EXPT** (Brotin et al. 2000)	67.0
MC (this work)	78.09



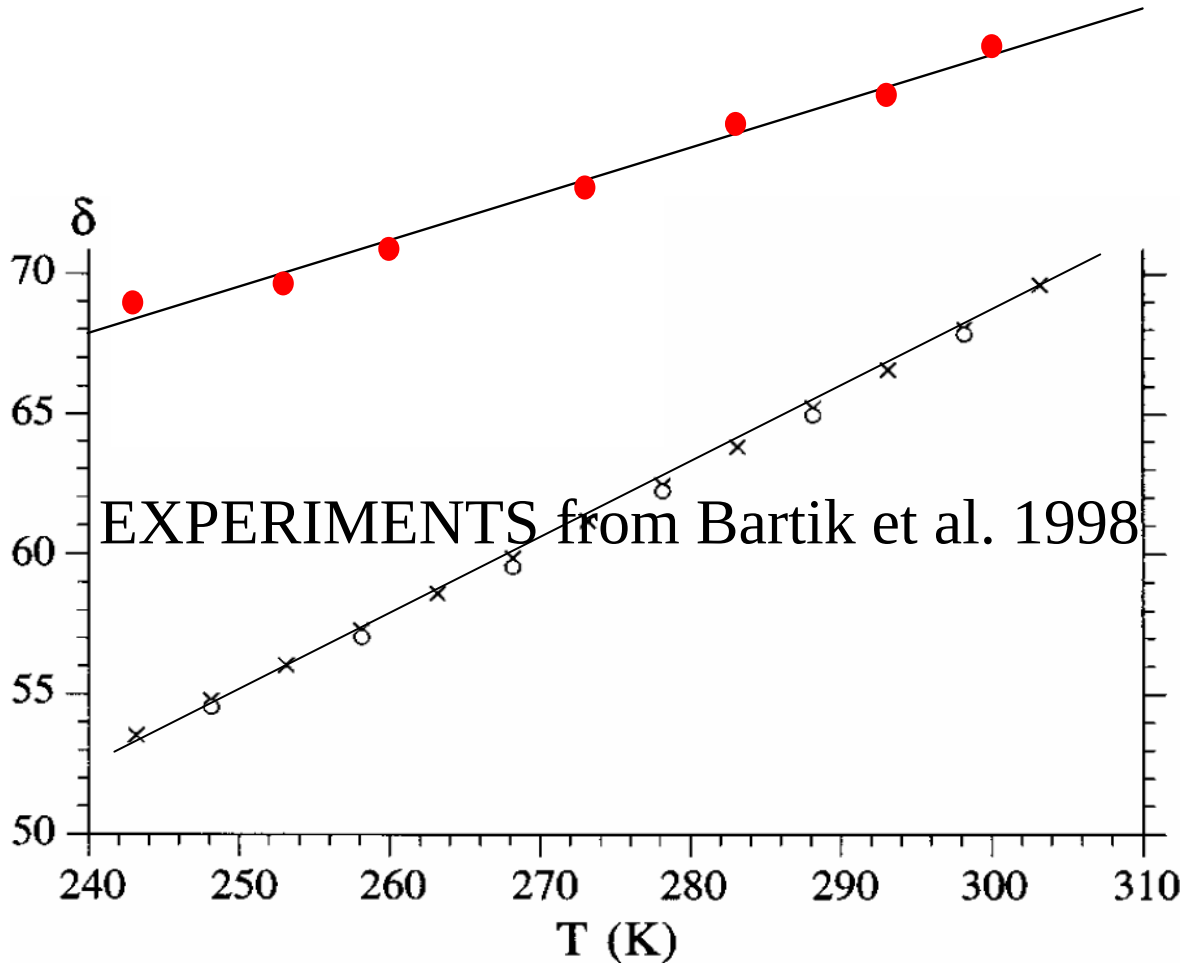
- Accept/reject displacements of xenon atom within the cage according to:

$$P_{acc} = \min [1, \exp(-\Delta U_{config}/k_B T)]$$

ΔU_{config} change in configurational energy

*T. Brotin, A. Lesage, L. Emsley, and A. Collet J. Am. Chem. Soc. 122, 1171 (2000).
K. Bartik, M. Luhmer, J. P. Dutasta, A Collet, and J. Reisse J. Am. Chem. Soc. 120, 784 (1998)

Temperature dependence of Xe@cryptoA not including cage deformation



Xe concentrations:

x nXe/nCA=0.46

o nXe/nCA=2.1

● **Monte Carlo SIMULATIONS**

---- D. N. Sears and C. J. Jameson, 2003

K. Bartik, M. Luhmer, J. P. Dutasta, A. Collet, and J. Reisse, J. Am. Chem. Soc. **1998**, 120, 784-791

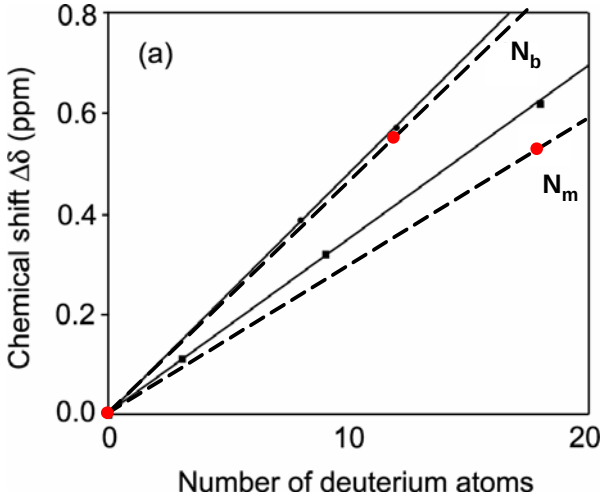
Our Monte Carlo SIMULATIONS

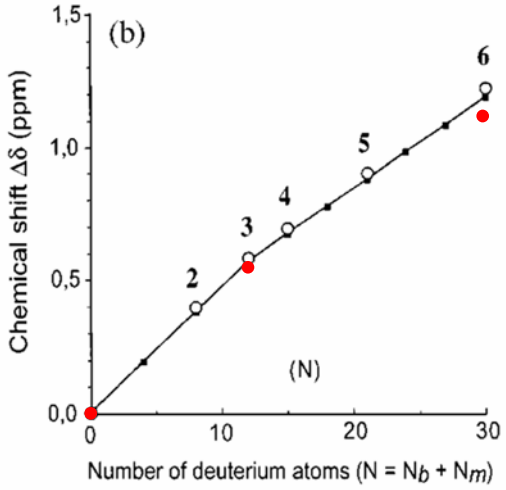
T, K	σ , ppm
300	78.77
293	76.35
283	75.31
273	73.04
260	70.73
253	69.62
243	68.94

Xe@d_n-cryptoA

EXPERIMENT

(Brotin et al. 2000)*



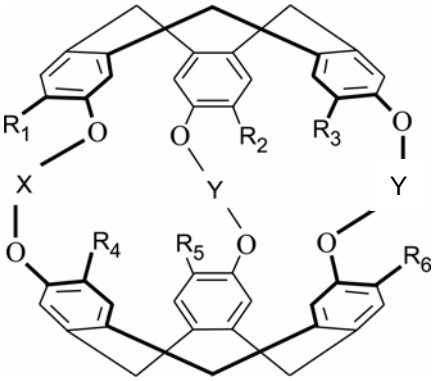


- **SIMULATIONS**

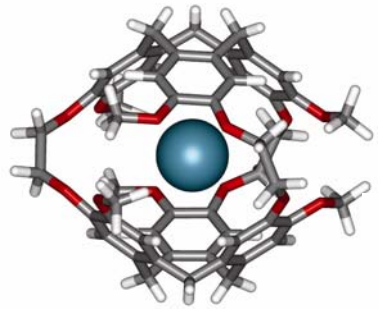
for example:

$<\sigma[Xe@cryptoA]>_{MC} - <\sigma[Xe@d_{30}\ cryptoA]>_{MC} = 1.118$ ppm

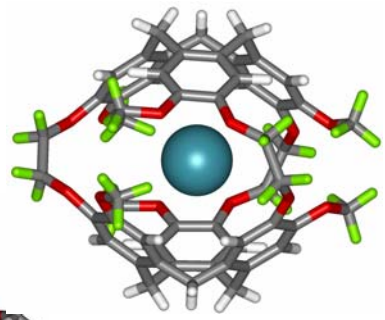
$r_0(Xe\text{-}H) - r_0(Xe\text{-}D) = 0.07$ Å



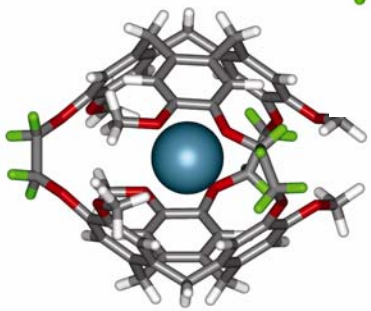
1: X = CH_2CH_2; Y = CH_2CH_2; R_1 = OCH_3; $R_2 - R_6$ = OCH_3
2: X = CH_2CH_2; Y = CD_2CD_2; R_1 = OCH_3; $R_2 - R_6$ = OCH_3
3: X = CD_2CD_2; Y = CD_2CD_2; R_1 = OCH_3; $R_2 - R_6$ = OCH_3
4: X = CD_2CD_2; Y = CD_2CD_2; R_1 = OCD_3; $R_2 - R_6$ = OCH_3
5: X = CD_2CD_2; Y = CD_2CD_2; $R_1 - R_3$ = OCD_3; $R_4 - R_6$ = OCH_3
6: X = CD_2CD_2; Y = CD_2CD_2; $R_1 - R_6$ = OCD_3



1



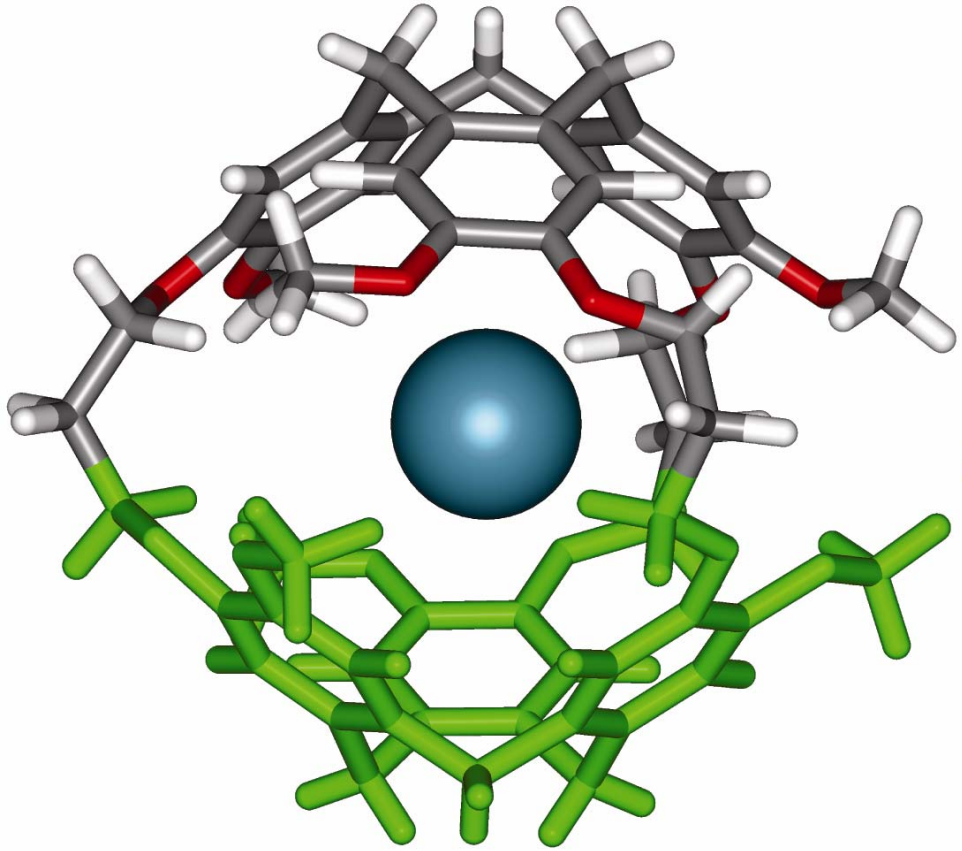
6



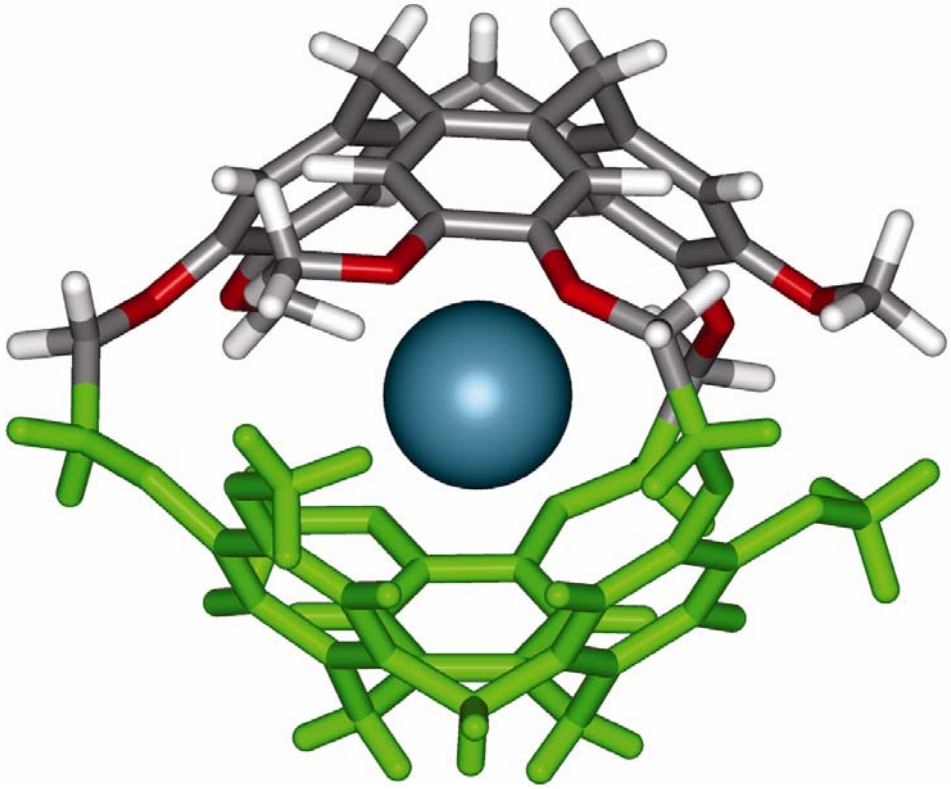
3

*T. Brotin, A. Lesage, L. Emsley, and A. Collet, J. Am. Chem. Soc. **2000**, 122, 1171-1174

Average structures of Xe@cryptoA and Xe@cryptoE



Xe@cryptoE

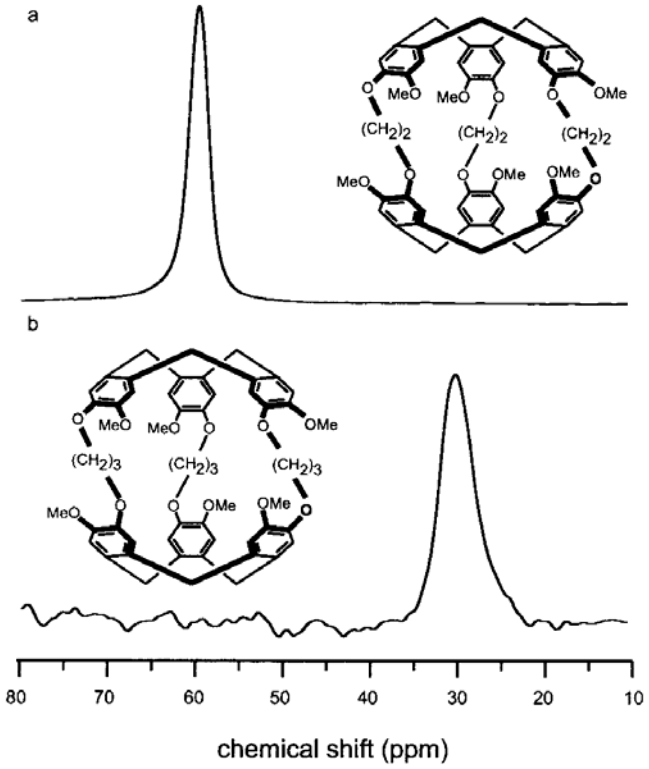


Xe@cryptoA

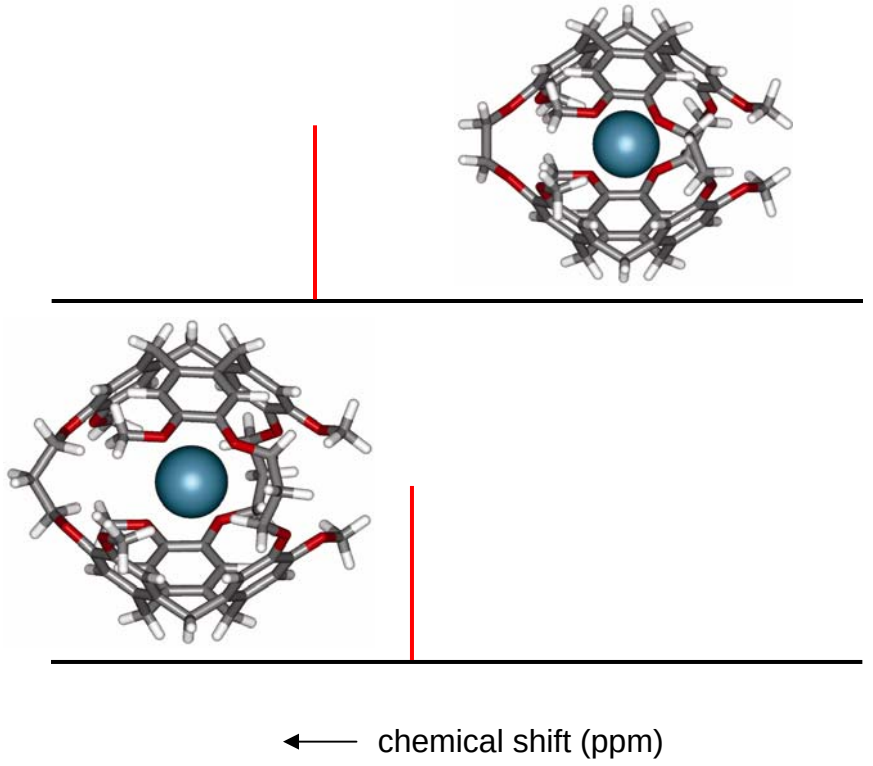
- Average structure of Xe@cryptoE arrived at using same method
- The same shielding surface can be used for both cages

Xe@cryptoA vs. Xe@cryptoE

Experiment (Pines et al. 2000)*



Our MC Simulations

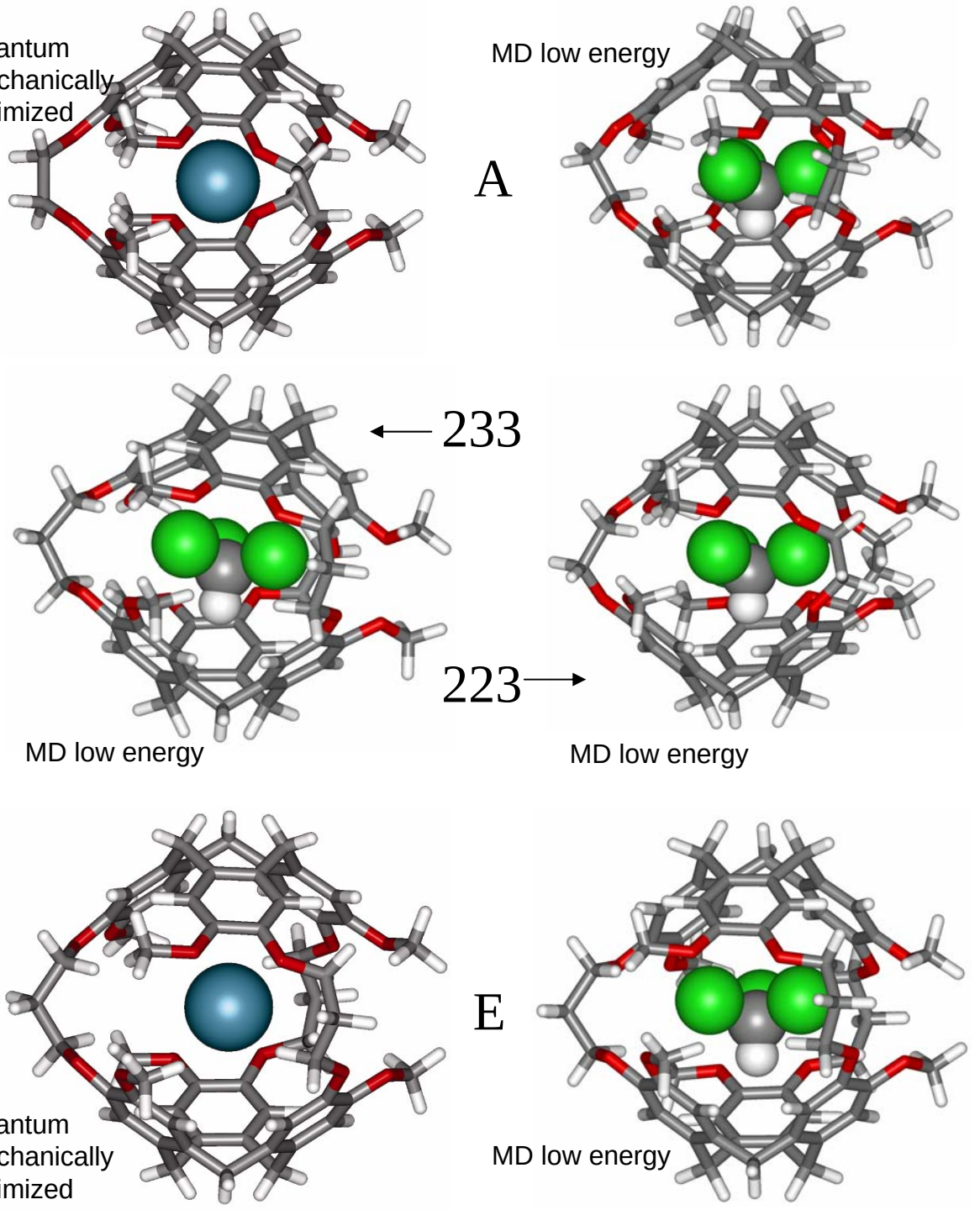


*M.M. Spence, S.M. Rubin, I.E. Dimitrov, E.J. Ruiz, D.E. Wemmer, A. Pines, S.Q. Yao, F. Tian, and P.G. Schultz, Proc. Nat. Acad. Sci. 98, 10654-10657 (2000).

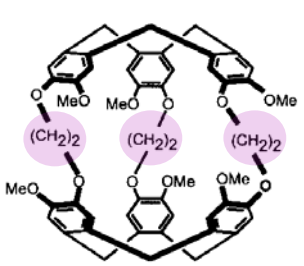
Determination of the solution structures of cryptophanes-223, and -233 by molecular dynamics simulations:

- Equilibration of solvent $(CHCl_2)_2$ at room temperature (120 molecules)
- Introduce cryptophane with guest to replace 5 $(CHCl_2)_2$ molecules
- Relax solvent around solute
- Simulated all-atom annealing
- MD to find low energy structure

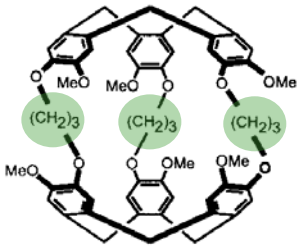
Quantum-mechanically optimized cryptophane-A and –E structures are used to calibrate the method using guests: CH_4, $CHCl_3$, CCl_4



^{129}Xe@cryptophanes

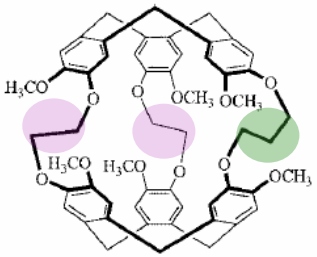


A



E

Pines et al.
Proc. Nat. Acad. Sci.
98, 10654 (2001)



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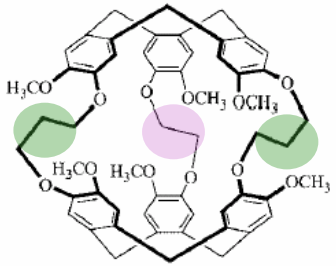

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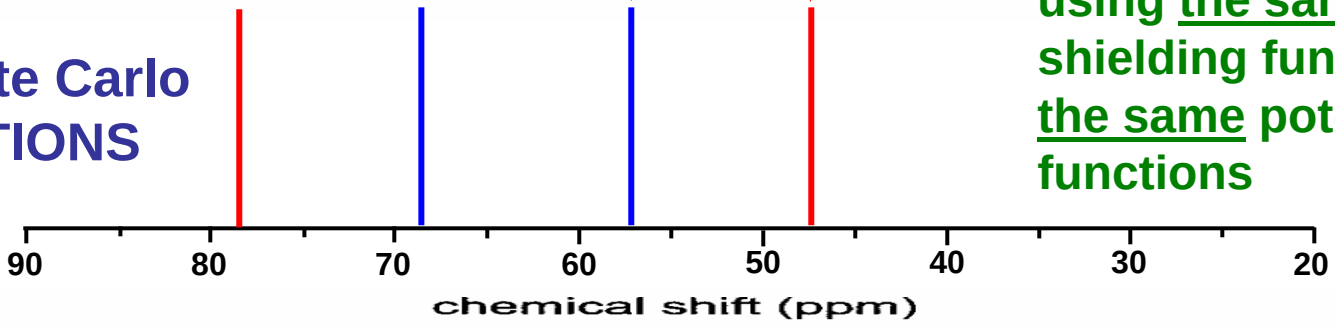
Brotin et al.
Eur. J. Org. Chem.
2003, 973-984

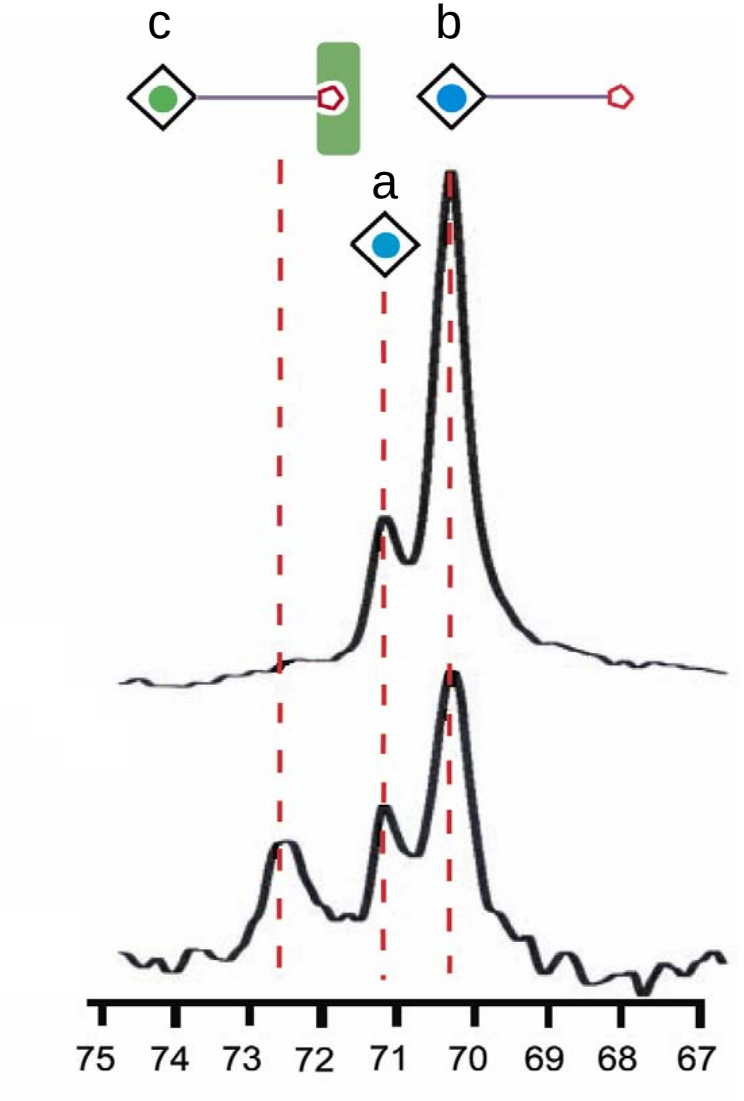
Our Monte Carlo SIMULATIONS



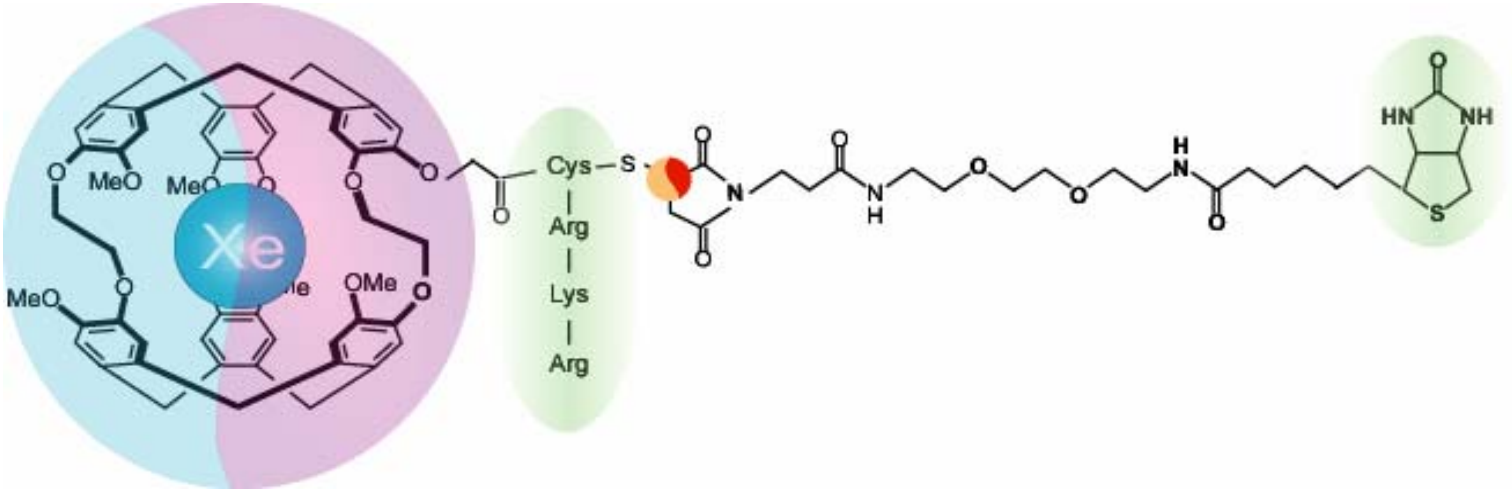
using the same shielding functions
the same potential functions

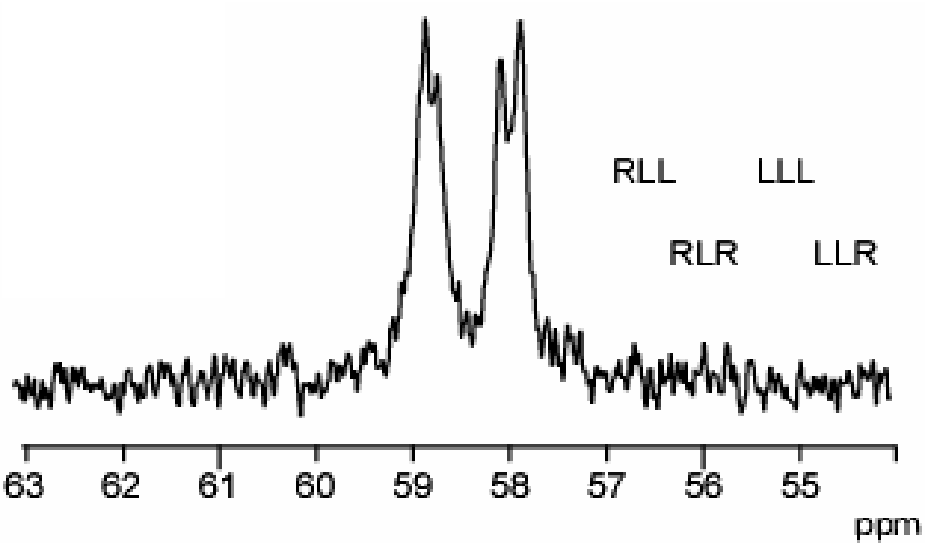
Comment on the Xe biosensor?

- Assume mechanical deformation of the cage, with no change in electronic factors
- a $\rightarrow$ b: MD of 2 cages linked by tether in the solvent
- a $\rightarrow$ c: MD of cage against a stationary polymer membrane representing the protein



Chiralization of Xe



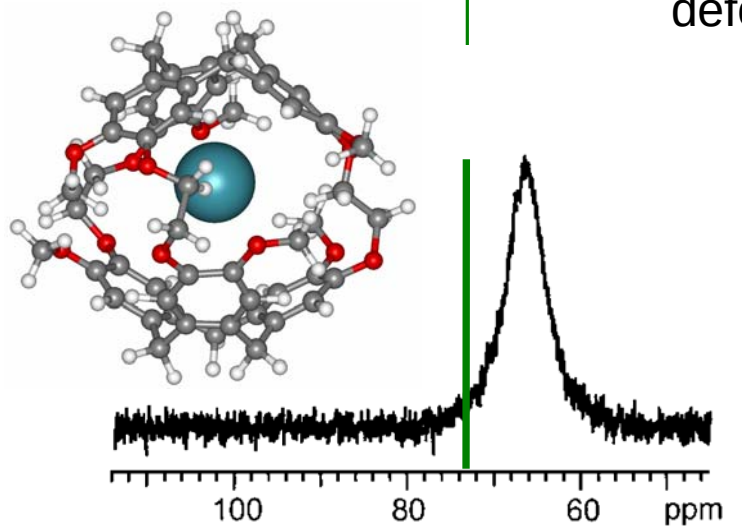


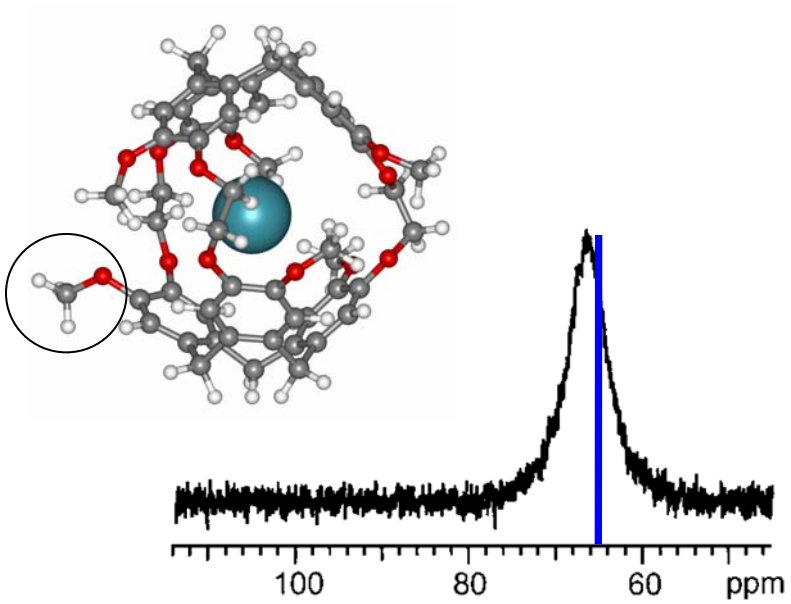
Chiral Center	Configuration			
Cage	L	L	R	R
Peptide	L	L	L	L
Asymmetric Carbon	L	R	L	R
Ligand	D	D	D	D

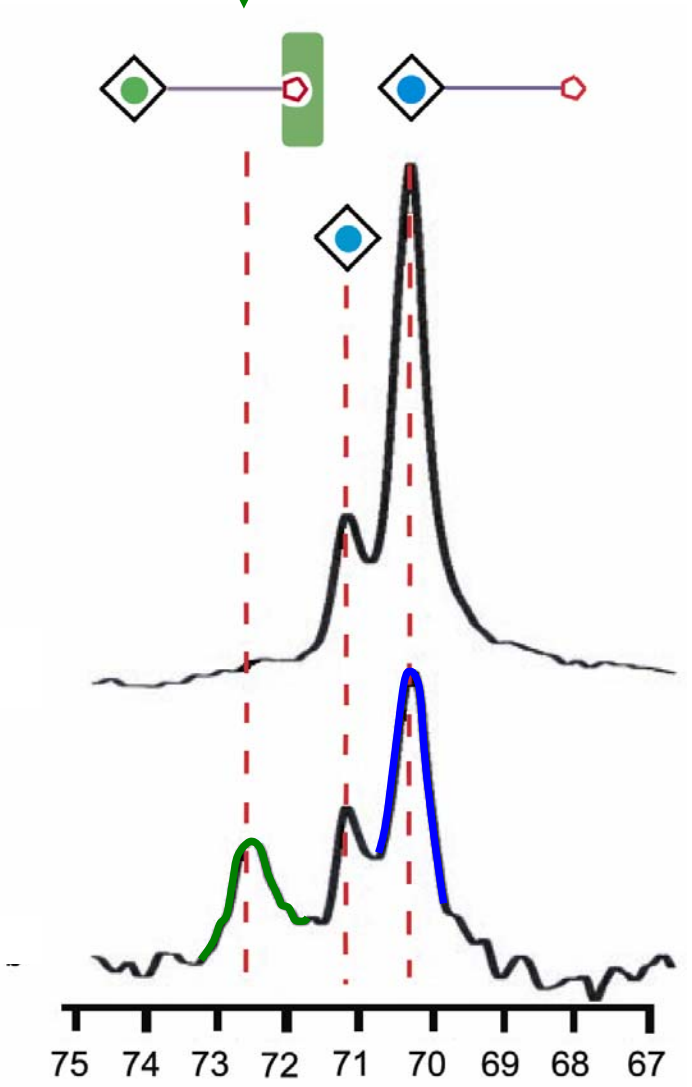
This slide courtesy of E. Janette Ruiz

E. Ruiz, M.M. Spence, D. E. Wemmer, A. Pines

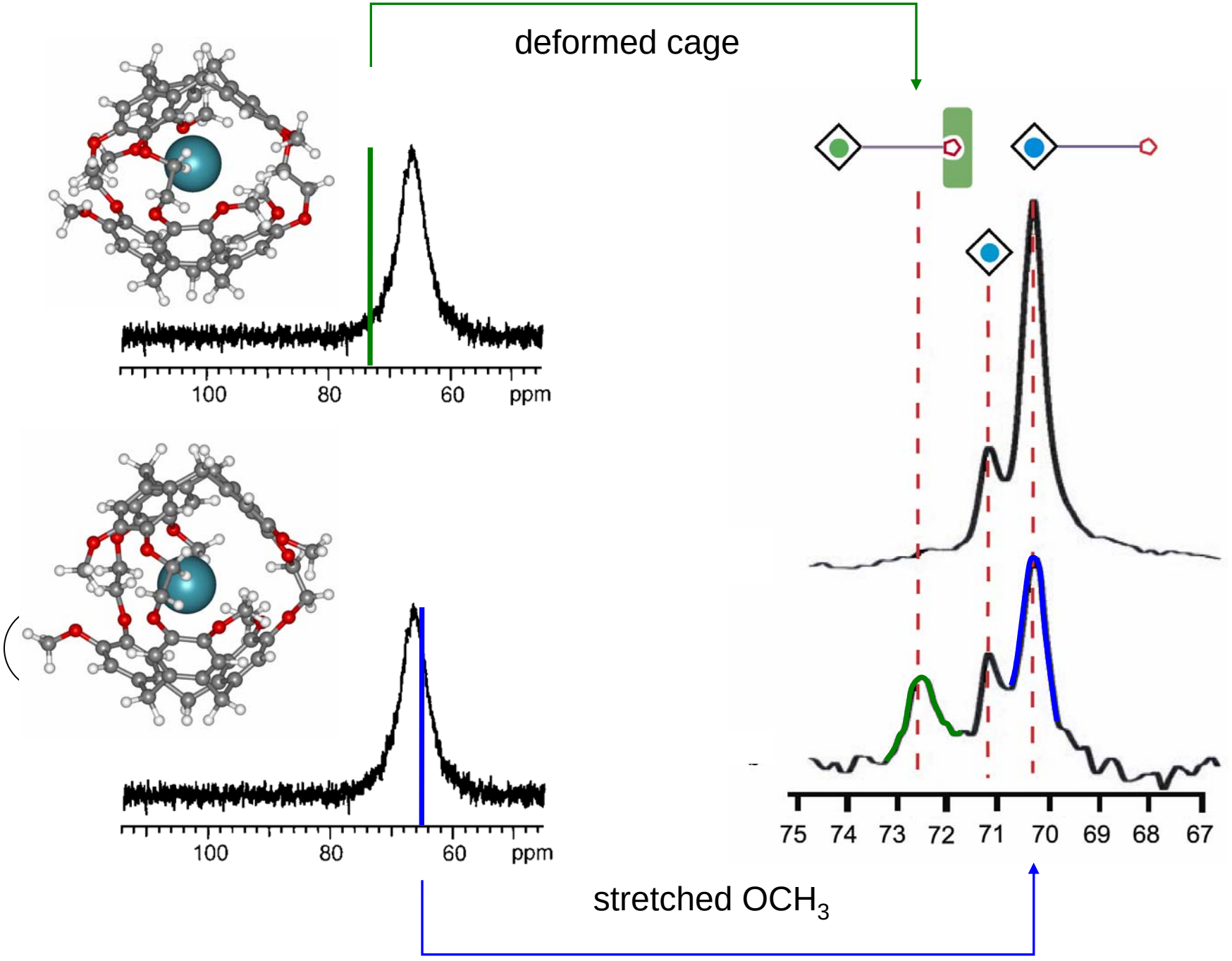
deformed cage

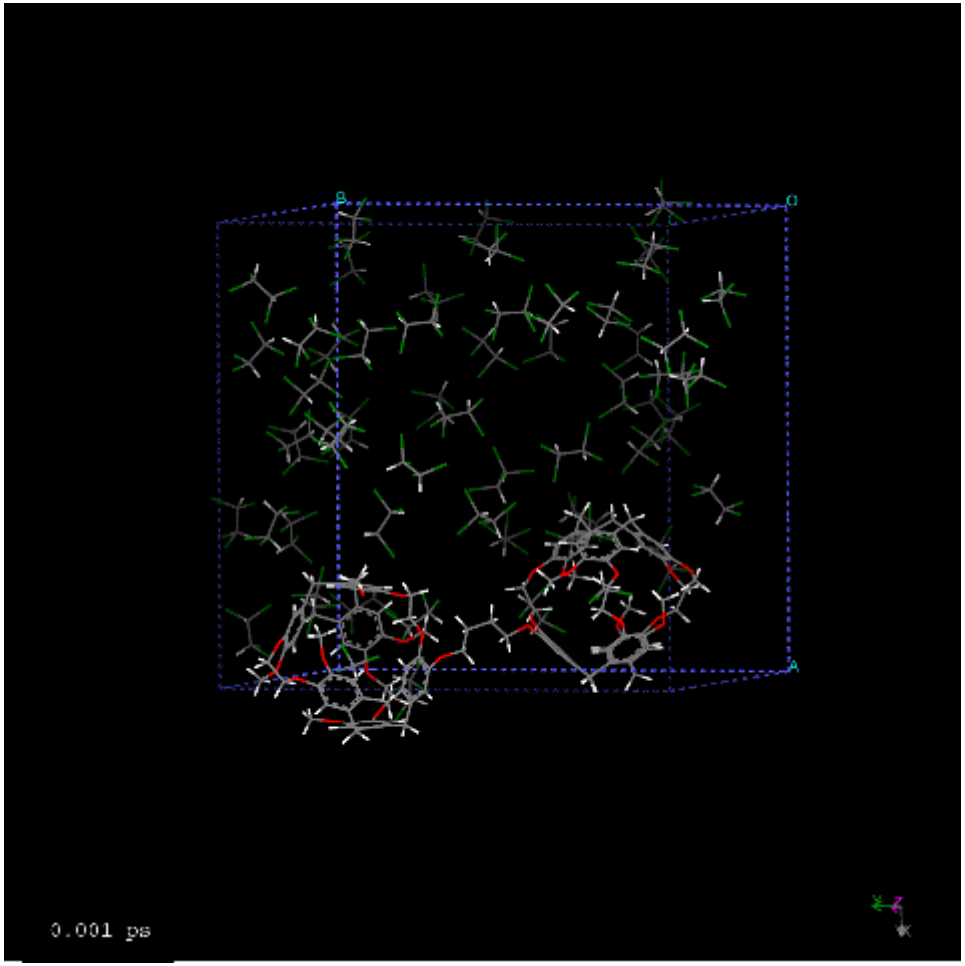


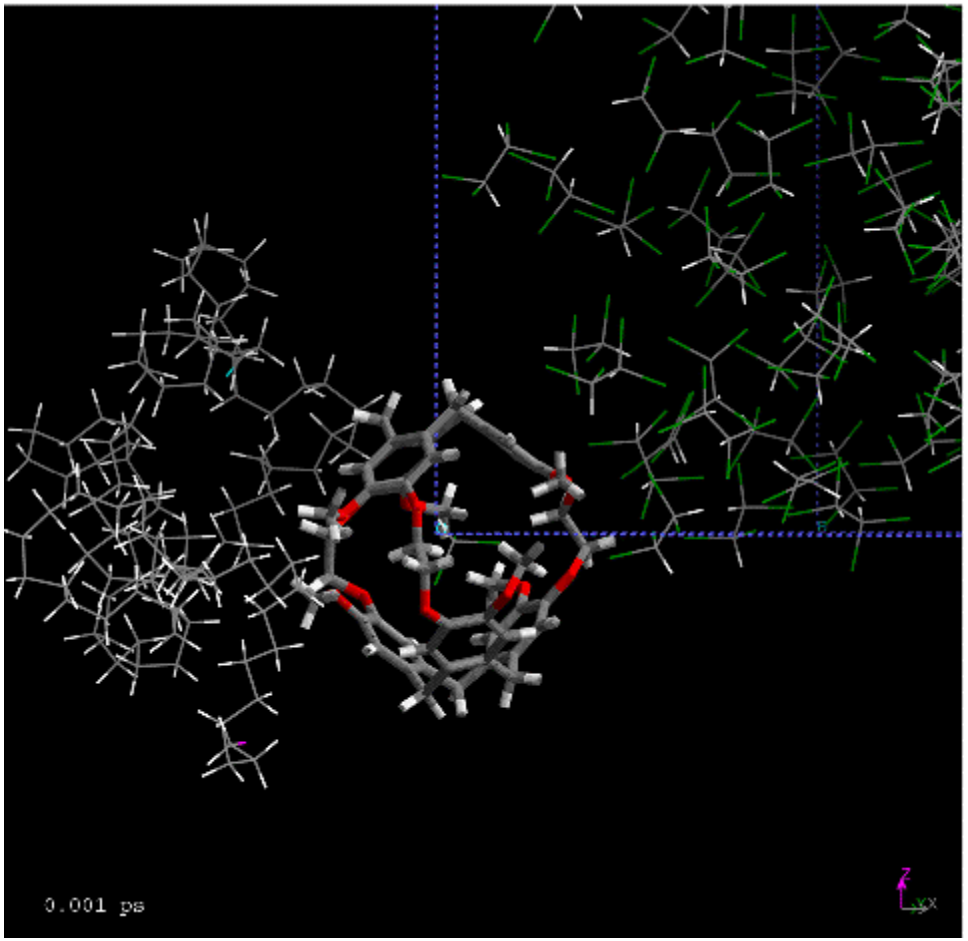




stretched OCH_3

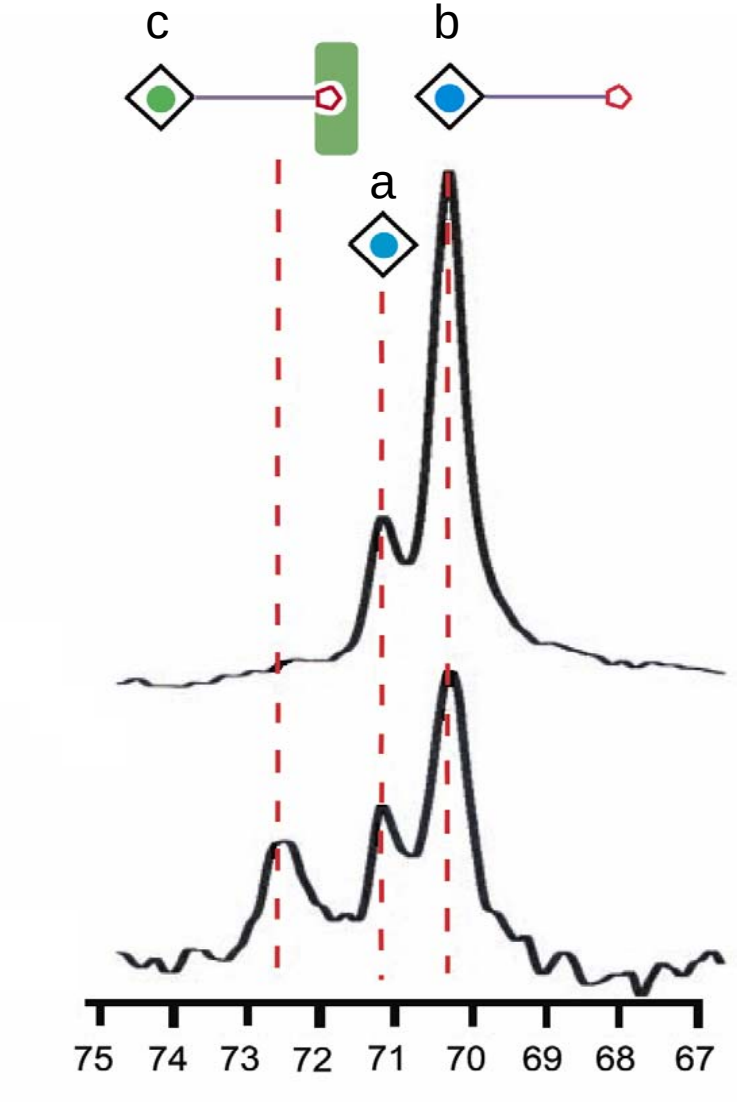

deformed cage
100
80
60
ppm
100
80
60
ppm
75
74
73
72
71
70
69
68
67
stretched OCH3


B
D
A
0.001 ps
Y
Z
X


0.001 ps

Comment on the Xe biosensor

- Mechanical deformation of the cage alone can account for sensing action with no change in electronic factors
- Xe shifts to more positive chemical shift upon binding
- longer tether → smaller shift; shorter tether → larger shift

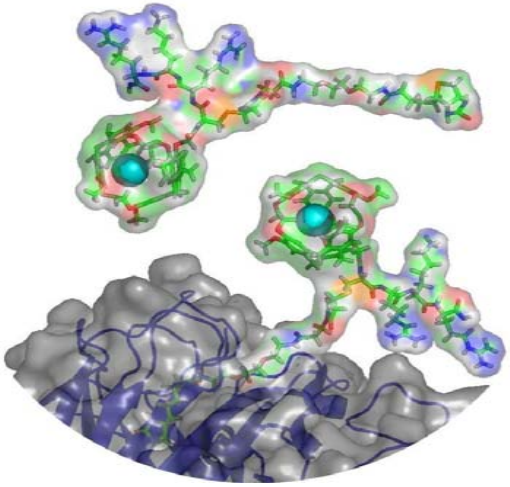


CONCLUSIONS

- Average structure in solution can not be obtained directly from X-Ray data
- Monte Carlo simulations reproduce
  a) the signs and relative magnitudes of the chemical shifts of Xe in cryptophanes-A, 223, 233, and E
  b) the sign and magnitude of the temperature coefficient for Xe@cryptophane-A
  c) the signs and magnitudes of the isotope effects for Xe@cryptophane-A
- Mechanism is proposed for sensing action: Upon binding, mechanical deformation of cage due to buffeting against the protein results in a smaller average inside volume for encapsulated Xe, thus a larger chemical shift; predict larger shift for shorter tether

Epilogue

Later experiments using various tether lengths prove our **larger Xe shift for shorter tether prediction**:

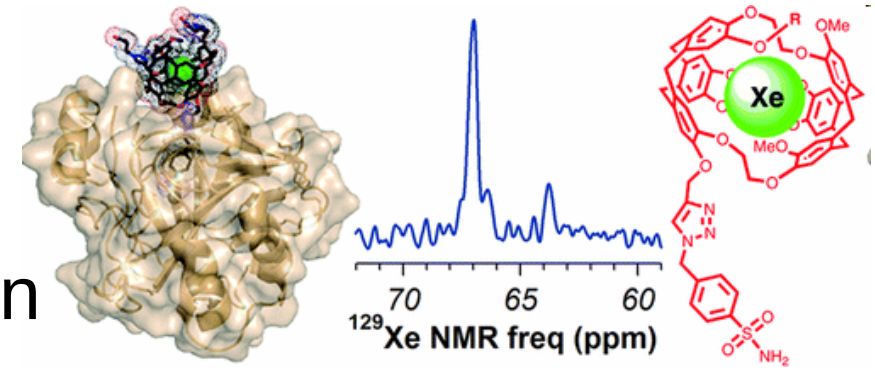


biosensor model courtesy of T. J. Lowery

Optimization of Xenon Biosensors for Detection of Protein Interactions, T. J. Lowery, S. Garcia, L. Chavez, E. J. Ruiz, T. Wu, T. Brotin, J. –P. Dutasta, D. S. King, . G. Schultz, A. Pines, D. E. Wemmer, *ChemBioChem* 7, 65-73 (2005).

Epilogue

Later experiments using Xe in a different functionalized crypto A binding to a different protein prove our prediction that **binding leads uniformly to a larger Xe chemical shift via the mechanical cage deformation upon binding**.



Cryptophane Xe-129 Nuclear Magnetic Resonance Biosensors Targeting Human Carbonic Anhydrase, J. M. Chambers, P. A. Hill, J. A. Aaron, Z. Han, D. W. Christianson, N. N. Kuzma and I. J. Dmochowski, *J. Am. Chem. Soc.*, 2009, 131 (2), 563–569

Epilogue

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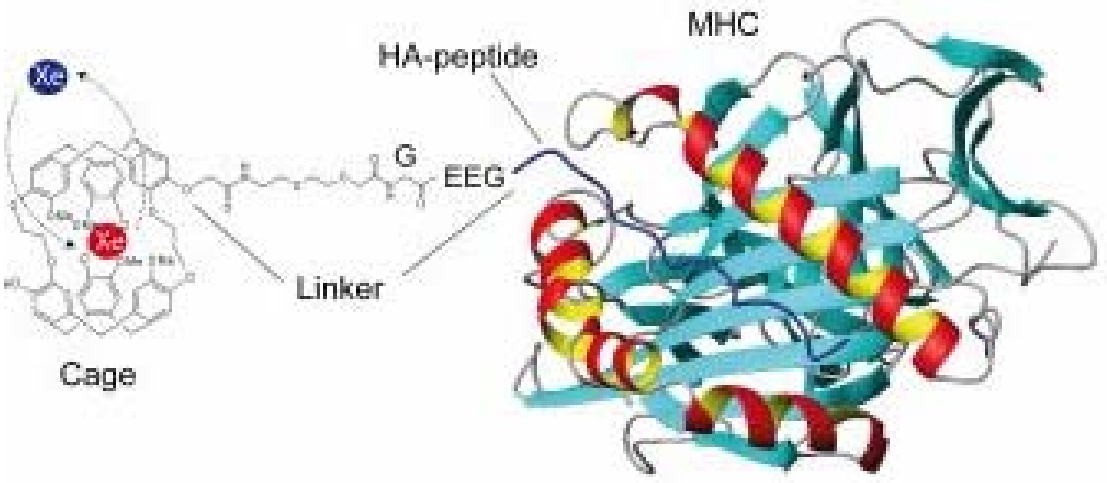

A Xe-129 Biosensor for Monitoring MHC-Peptide Interactions, A. Schlundt, W. Kilian, M.Beyermann, J. Sticht, S. Günther, S. Höpner, K. Falk, O. Roetzschke, L. Mitschang, C. Freund,Angew. Chem. Intl. Ed. 48**,** 4142 –4145 (2009)

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This work was begun while CJJ was Miller Visiting Professor at the University of California – Berkeley in the laboratory of Alex Pines.

Unpublished X-ray structure of cryptophane-A was provided by Professor J. P. Dutasta