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Chirality and shielding: from helices to Xe biosensor

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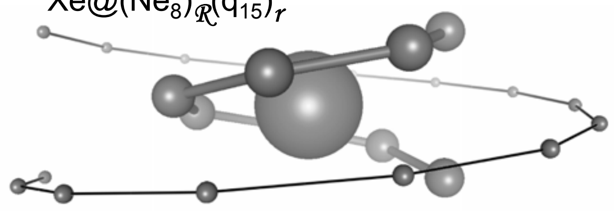
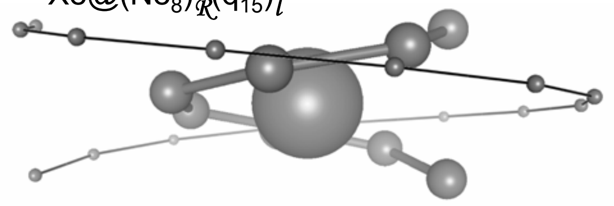
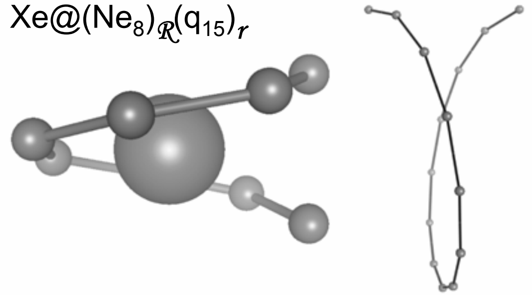
Xe@(Ne$_8$)$_{\mathcal{R}}$(q$_{15}$)$_r$



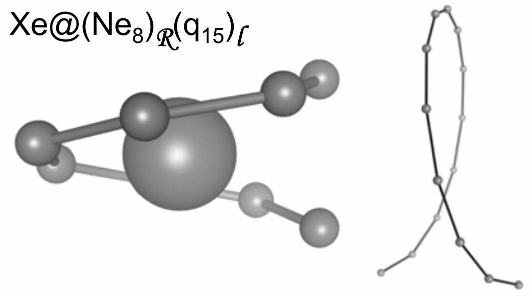
Xe@(Ne$_8$)$_{\mathcal{R}}$(q$_{15}$)$_\ell$

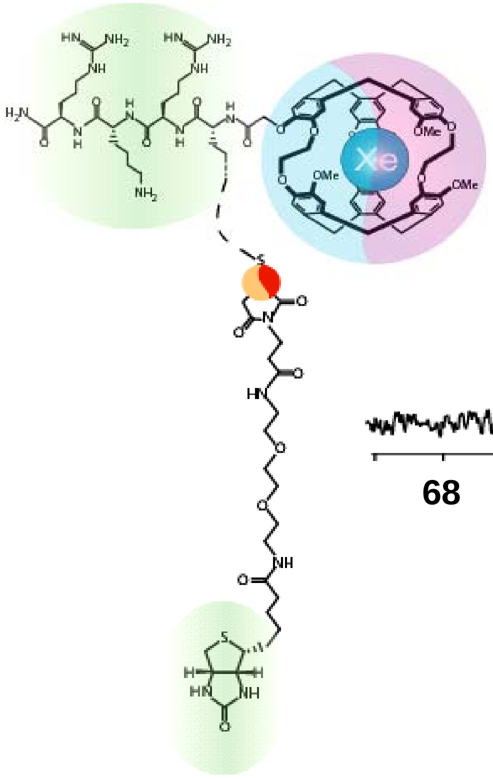


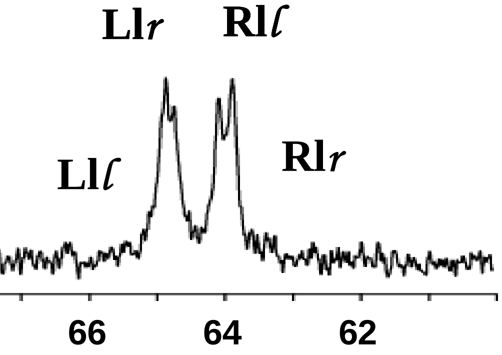
Xe@(Ne$_8$)$_{\mathcal{R}}$(q$_{15}$)$_r$



Xe@(Ne$_8$)$_{\mathcal{R}}$(q$_{15}$)$_\ell$







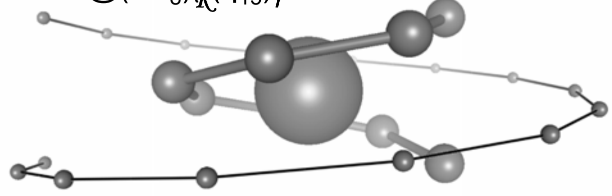
Questions:

- How do the shielding tensors of mirror image molecules differ?
- What are the measures of induced chirality of a Xe atom in a chiral environment and also in the chiral field of other asymmetric groups?

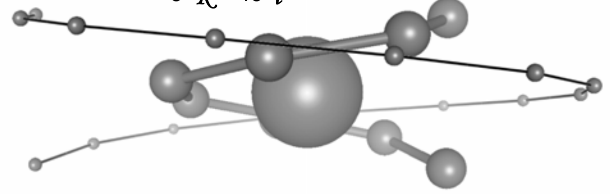
A series of studies of the nuclear magnetic shielding tensor in chiral and diastereomeric systems:

- **The shielding tensor of Xe interacting with Ne helices**
- **The shielding tensor of a naked spin in Ne helices**
- **The single electron on a helix model**
- **The odd and even character of the shielding response to a chiral potential**

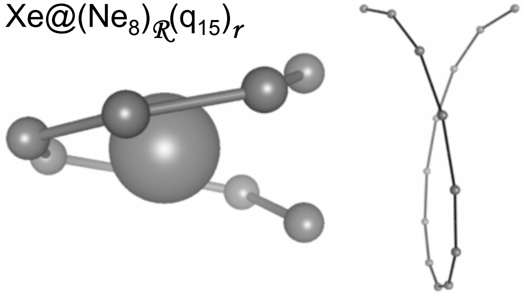
$\mathrm{Xe@(Ne_8)}_{\mathcal{R}}(\mathrm{q}_{15})_r$



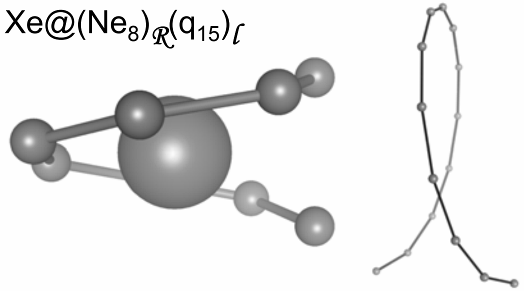
$\mathrm{Xe@(Ne_8)}_{\mathcal{R}}(\mathrm{q}_{15})_\ell$



$\mathrm{Xe@(Ne_8)}_{\mathcal{R}}(\mathrm{q}_{15})_r$



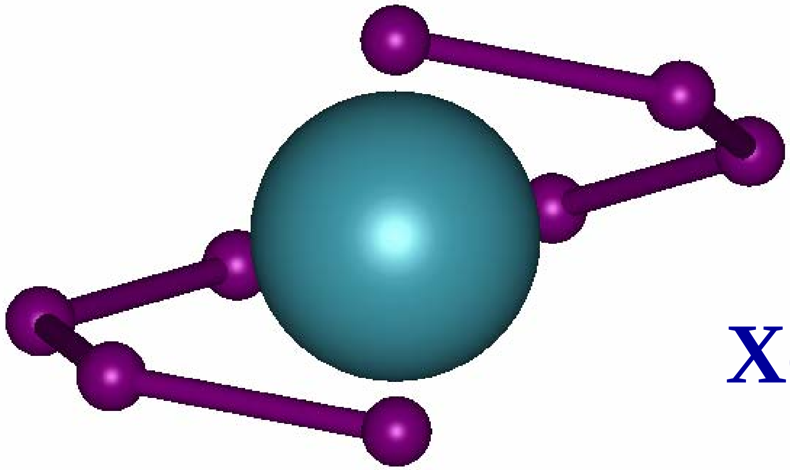
$\mathrm{Xe@(Ne_8)}_{\mathcal{R}}(\mathrm{q}_{15})_\ell$



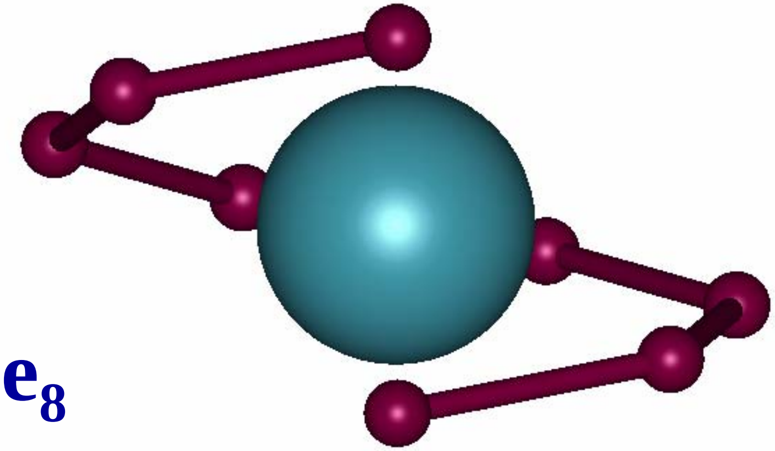
How do the shielding tensors of mirror image molecules differ?

Compare shielding σ tensor

for Xe in a left-handed Ne_8 helix
vs. Xe in a right-handed Ne_8 helix



Xe@Ne_8



Xe in a left handed helix (L)

Xe in a right handed helix (R)

Left-handed vs. right-handed: what do the tensors look like?

Xe shielding tensor, nuclear site symmetry is C_2

Xe@Ne$_8$(**R**) and Xe@Ne$_8$(**L**)

full tensor

-56.4483	0	0
0	-59.0913	**-12.4742**
0	**-12.5330**	-91.2904

-56.4483	0	0
0	-59.0913	**12.4742**
0	**12.5330**	-91.2904

symmetric tensor

-56.4483	0	0
0	-59.0913	**-12.5036**
0	**-12.5036**	-91.2904

-56.4483	0	0
0	-59.0913	**12.5036**
0	**12.5036**	-91.2904

antisymmetric tensor

0	0	0
0	0	**+0.0294**
0	**-0.0294**	0

0	0	0
0	0	**-0.0294**
0	**+0.0294**	0

How do the shielding tensors of mirror image molecules differ?

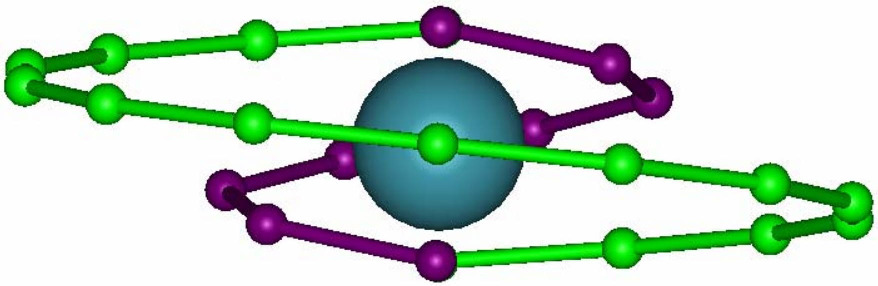
All elements are IDENTICAL,
***EXCEPT* that corresponding**
off-diagonal elements
have opposite signs
in the full tensor,
in the symmetric part of the tensor
and in the antisymmetric part of the tensor

Diastereomers

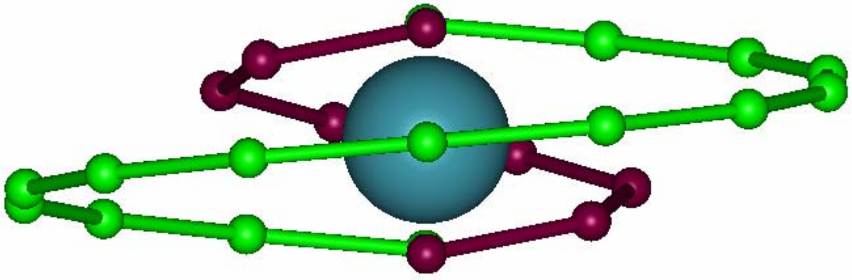
What do the tensors look like?

Model Systems Xe@Ne$_8$(+q)$_{15}$

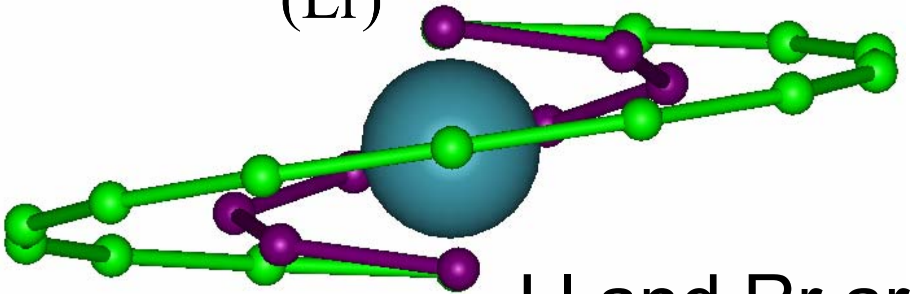
(Ll)



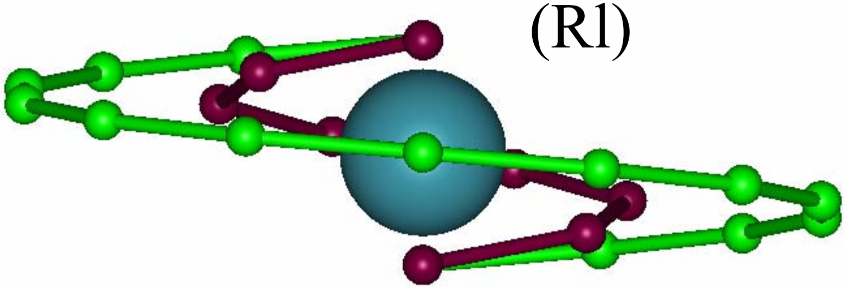
(Rr)



(Lr)



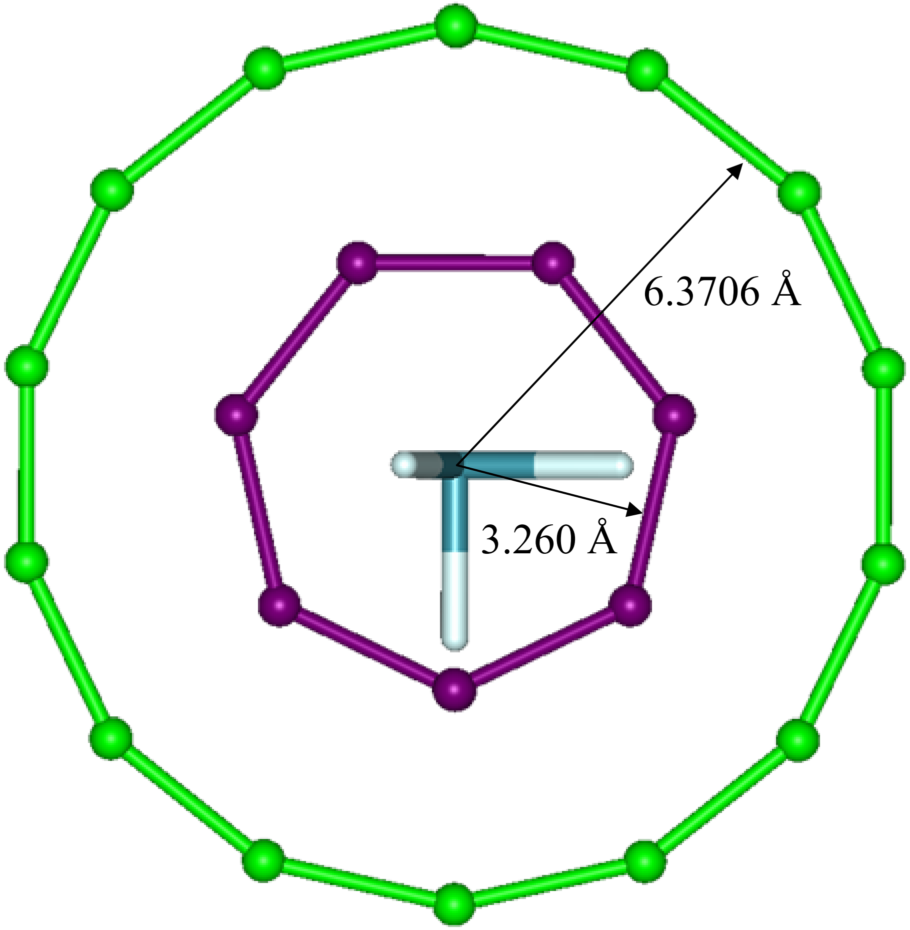
(Rl)



Ll and Rr are mirror images

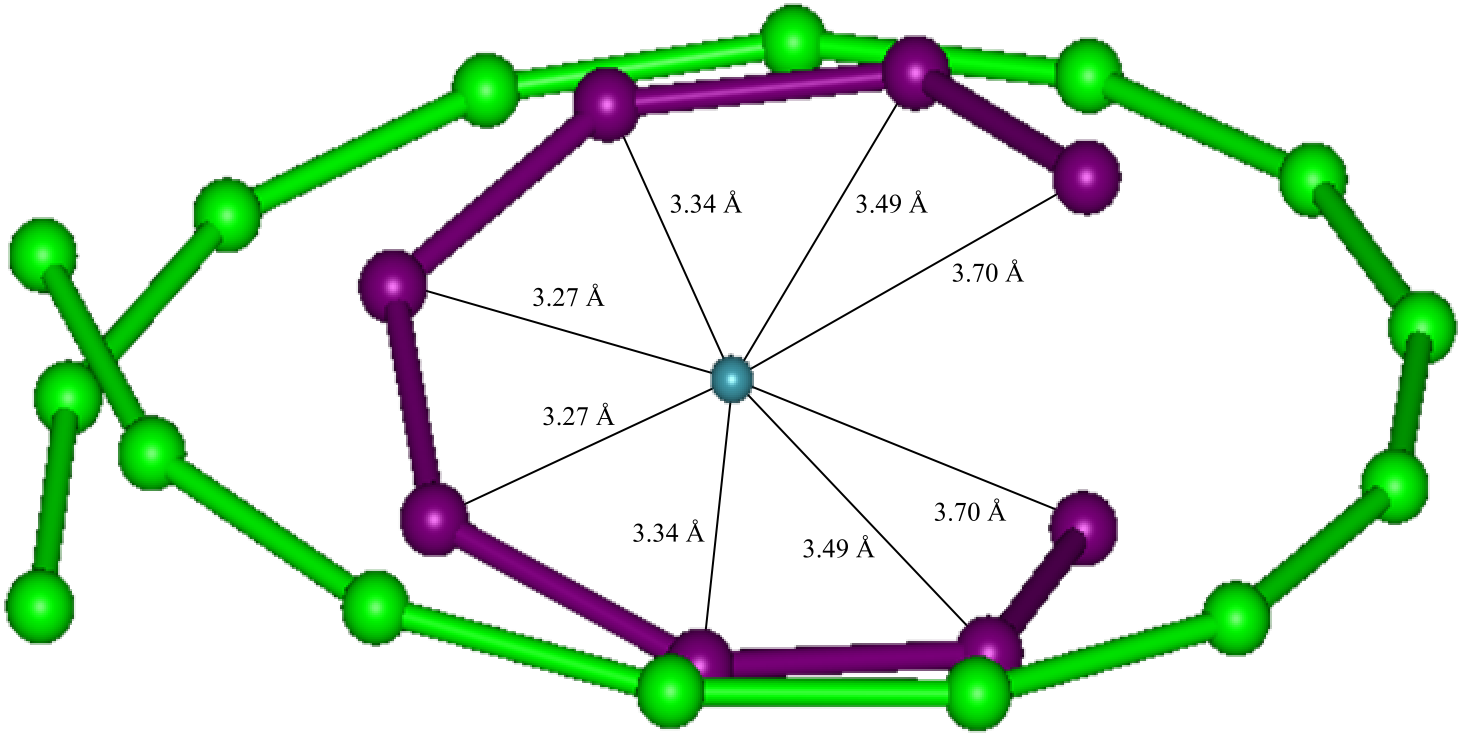
Lr and Rl are mirror images

Ll and Lr are diastereomers

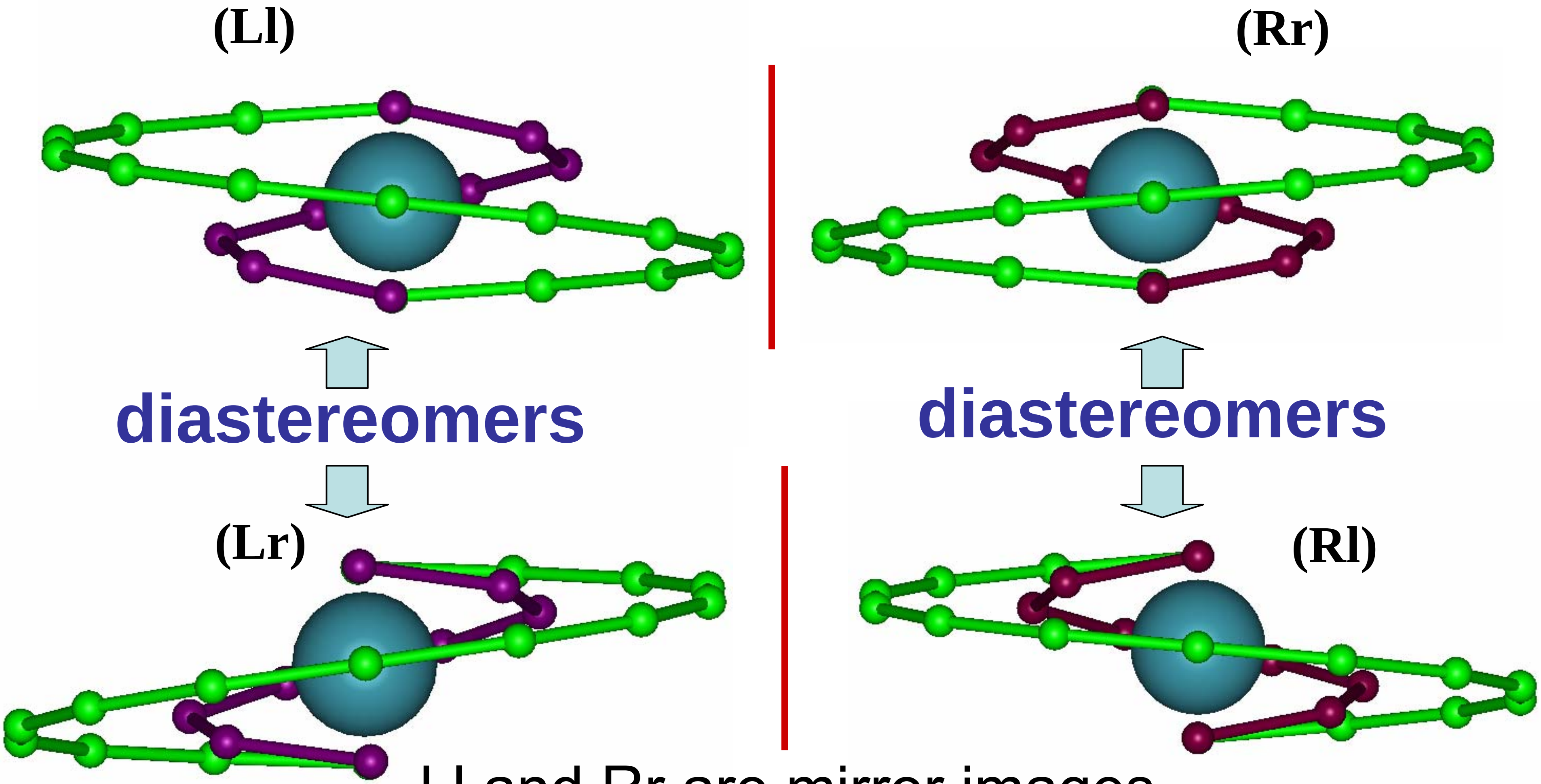


Pitch = 2π(0.557042)
b=0.557042

Model System $Xe@Ne_8(+q)_{15}$ (Ll)



Model Systems Xe@$Ne_8(+q)_{15}$



(Ll)

(Rr)

diastereomers

diastereomers

(Lr)

(Rl)

Ll and Rr are mirror images

Lr and Rl are mirror images

Ll and Lr are diastereomers

Diastereomers $\sigma[Xe@Ne_8(+q)_{15}]$

Mirror images: what do the tensors look like?

Rr

-15.6121	0	0
0	-17.3762	**-4.5346**
0	**-3.7095**	-29.7162

Ll

-15.6121	0	0
0	-17.3762	**+4.5346**
0	**+3.7095**	-29.7162

Rl

-14.5921	0	0
0	-16.9236	**-4.1914**
0	**-3.8906**	-28.3861

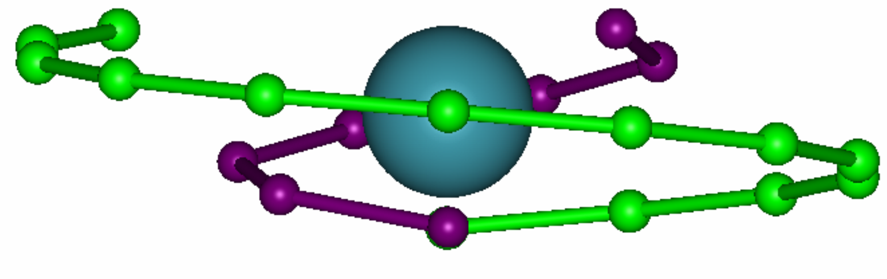
Lr

-14.5921	0	0
0	-16.9236	**4.1914**
0	**+3.8906**	-28.3861

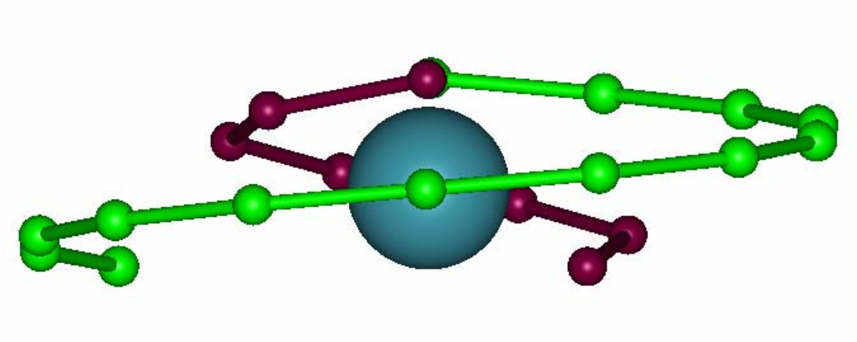
Tensors of Rr and Ll are experimentally indistinguishable since only the signs of off-diagonal tensor components are different; ditto for Rl and Lr.

Another example: Model Systems Xe@Ne$_7$(+q)$_{13}$

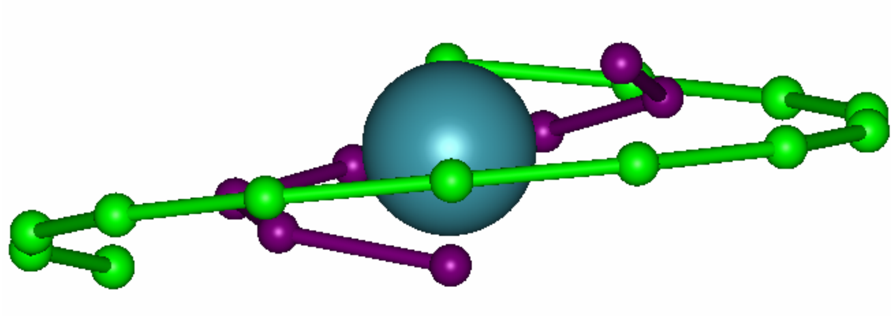
(L) in a Left handed PCA (Ll)



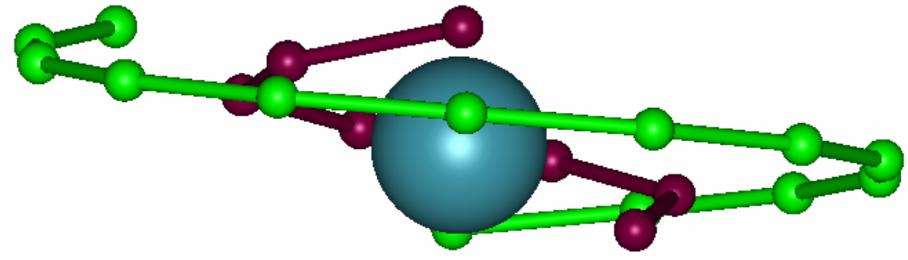
(R) in a right handed PCA (Rr)



(L) in a right handed PCA (Lr)



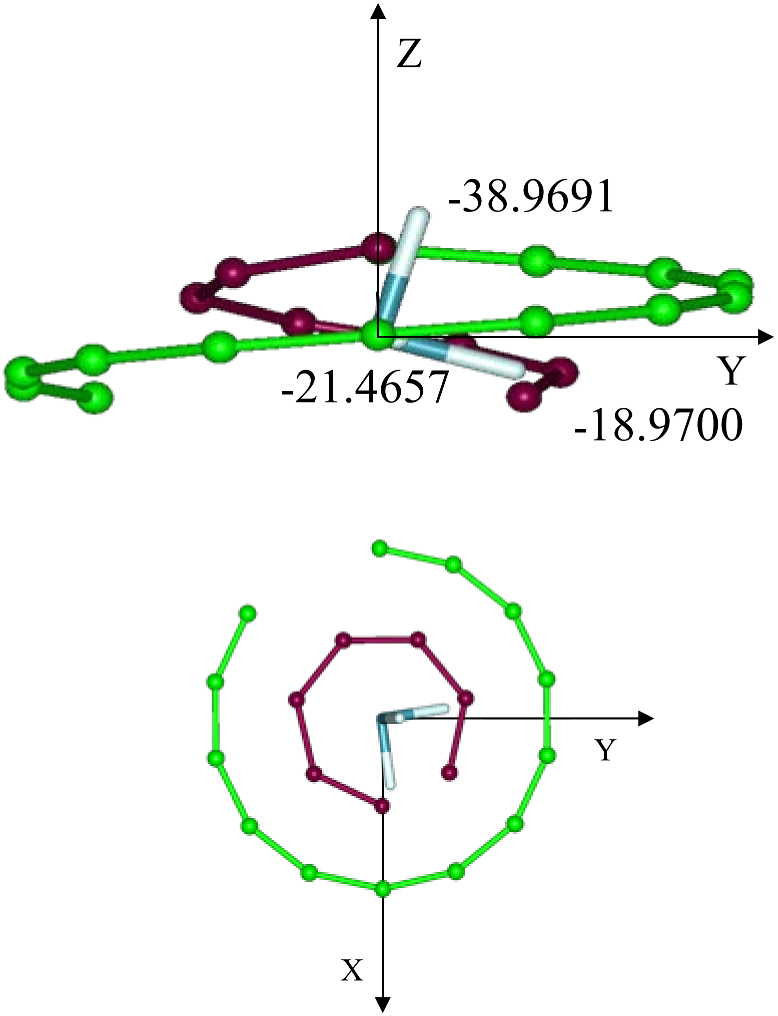
(R) in a left handed PCA (Rl)



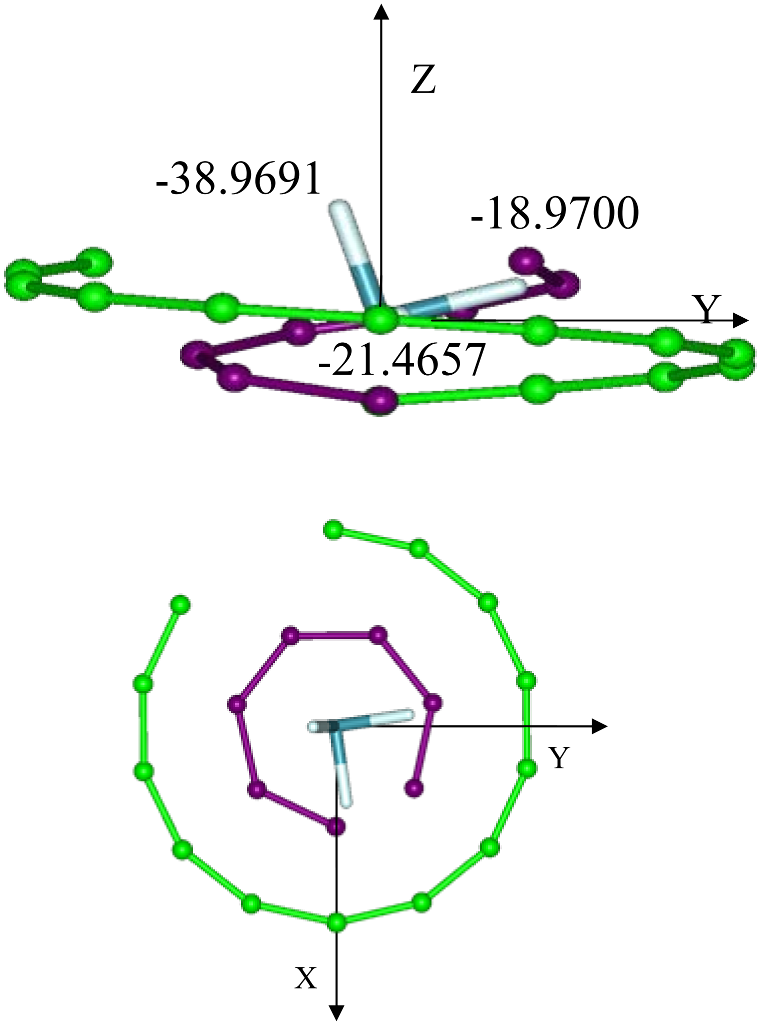
$Xe@Ne_7(+q)_{13}$

$\sigma_{isotropic} = -26.4683$

Rr



Ll



Diastereomers $Xe@Ne_7 \cdot q_{13}$
Mirror images: what do the tensors look like?

(**Rr**) nuclear site symmetry is C_1 (**Ll**)

full tensor

-21.4184	-0.2301	0.6066
-0.3583	-20.6056	-5.7792
-0.1738	-5.0188	-37.3808

-21.4184	-0.2301	-0.6066
-0.3583	-20.6056	5.7792
0.1738	5.0188	-37.3808

symmetric tensor

-21.4184	-0.2942	0.2164
-0.2942	-20.6056	-5.3990
0.2164	-5.3990	-37.3808

-21.4184	-0.2942	-0.2164
-0.2942	-20.6056	5.3990
-0.2164	5.3990	-37.3808

antisymmetric tensor

0	0.0641	0.3902
-0.0641	0	-0.3802
-0.3902	0.3802	0

0	0.0641	-0.3902
-0.0641	0	0.3802
0.3902	-0.3802	0

How do the shielding tensors of mirror image molecules differ?

All elements are IDENTICAL,
***EXCEPT* that corresponding**
off-diagonal elements
have <u>opposite signs</u>
in the full tensor,
in the symmetric part of the tensor
and in the antisymmetric part of the tensor

Measures of induced chirality of Xe:

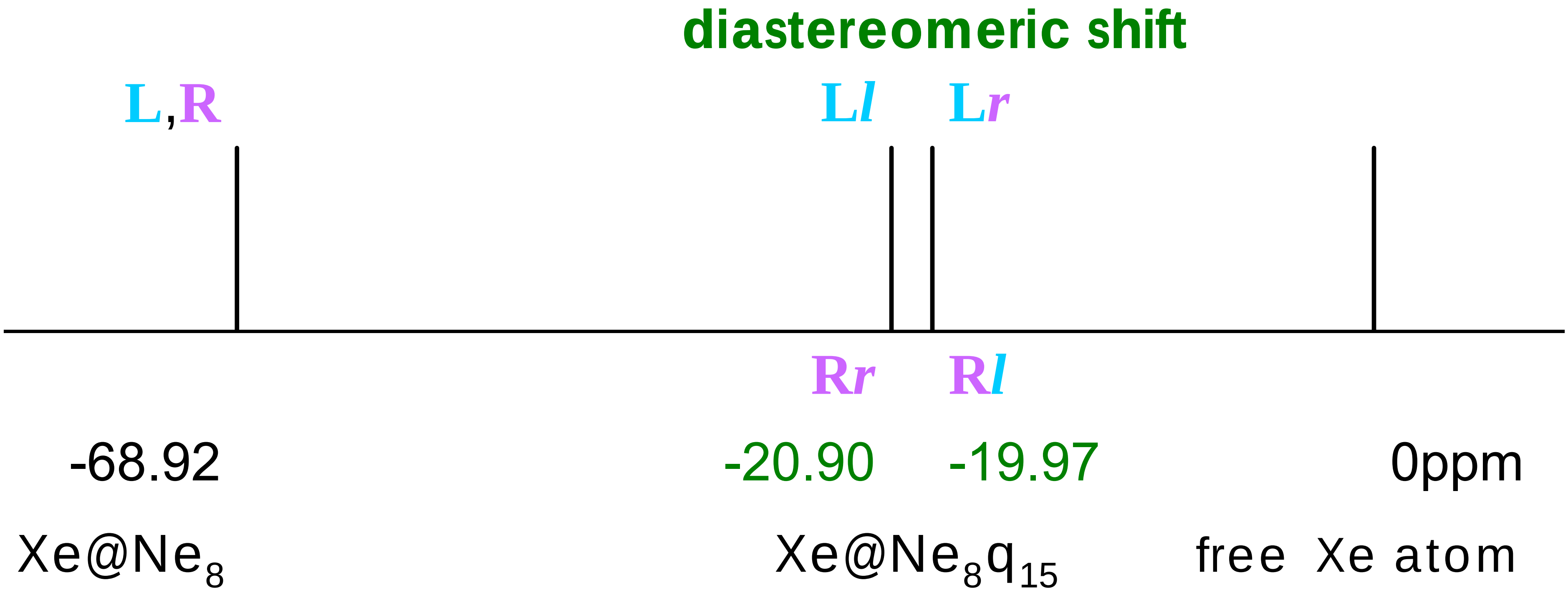
- non-zero antisymmetric tensor elements, 0.4126 and 0.1504 ppm for (Rr) and (Rl) respectively; non-vanishing but difficult to measure experimentally

- chemical shift between diastereomers
  -0.9342 ppm for (Rr) – (Rl)
  appears as a splitting

Isotropic ^{129}Xe shielding, ppm

Model	$Xe@Ne_7(+q)_{13}$	$Xe@Ne_8(+q)_{15}$	$Xe@Ne_{15}$
L, R	-64.7656	-68.9434	-75.817
Rr, Ll	-26.4683	-20.9015	
Lr, Rl	-25.5027	-19.9673	
diastereo-meric shift (Ll - Lr) or (Rr - Rl)	-0.9656	-0.9342	

^{129}Xe NMR spectrum of Xe in Ne helices



diastereomeric shift

L,**R**

L*l* **L*r***

R*r* **R*l***

-68.92 -20.90 -19.97 0ppm

Xe@Ne$_8$

Xe@Ne$_8$q$_{15}$

free Xe atom

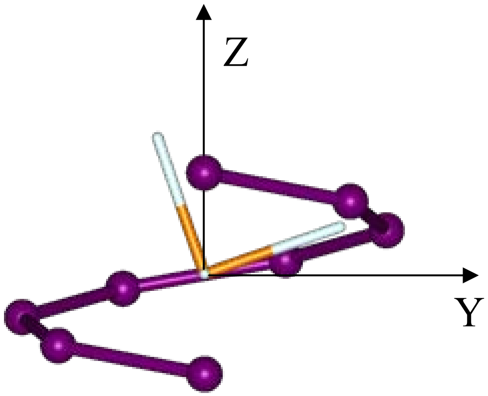
D.N. Sears, C. J. Jameson, R. A. Harris, J. Chem. Phys. 119, 2685 (2003)

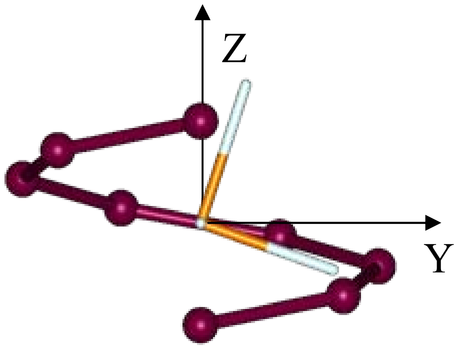
CONCLUSIONS I:

- Chiral potential provided by point charge helix is sufficient to provide a diastereomeric shift for Xe atom of the right order of magnitude to be observable in the ^{129}Xe NMR spectrum.

- Therefore, can calculate Xe shielding at center of the chiral cryptophane cage attached to chiral tethers by using point charges to represent the atoms of the tether.

II. Shielding tensor of a **naked spin** in Ne_8 helices





II. Shielding tensor of a naked spin in Ne_8 helices

Examine the molecular shielding of the chiral system itself. This is the shielding that can be mapped by placing a magnetic moment anywhere around (or in) the molecule.

GOALS: To find out

- To what extent does the molecular shielding tensor reflect its chiral character?
- Is the sign of the shift between diastereomers related to the same or opposite handedness of the two chiral systems that make the diastereomeric pair?

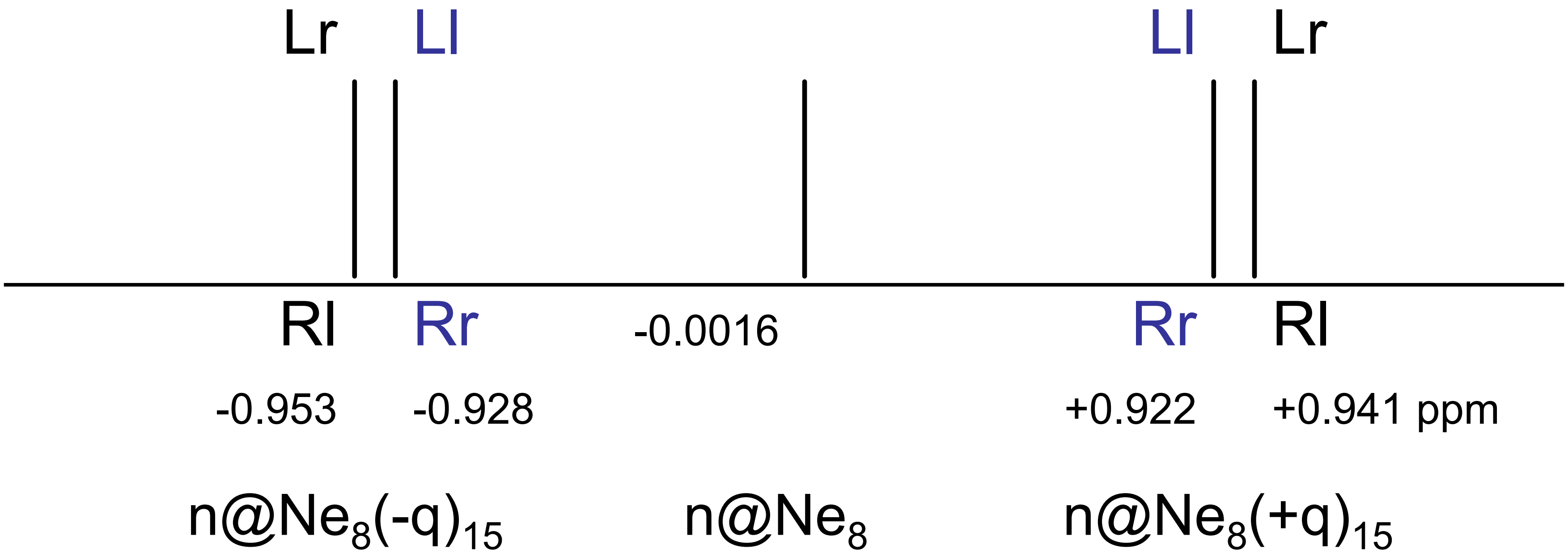
Isotropic shielding of a naked spin in chiral systems

System	Mirror image system	σ_{iso}, ppm
n@Ne_8 (**L**)	n@Ne_8 (**R**)	-0.0016
[n@Ne_8·$(+q)_{15}$] (**Ll**)	[n@Ne_8·$(+q)_{15}$] (**Rr**)	+0.9218
[n@Ne_8·$(+q)_{15}$] (**Rl**)	[n@Ne_8·$(+q)_{15}$] (**Lr**)	+0.9409
[n@Ne_8·$(-q)_{15}$] (**Ll**)	[n@Ne_8·$(-q)_{15}$] (**Rr**)	-0.9277
[n@Ne_8·$(-q)_{15}$] (**Rl**)	[n@Ne_8·$(-q)_{15}$] (**Lr**)	-0.9535

Diastereomeric shifts:

[n@Ne_8·$(+q)_{15}$]	Ll - Lr	-0.0191
[n@Ne_8·$(-q)_{15}$]	Ll - Lr	+0.0258

NMR spectrum of a naked spin in Ne helices



Lr Ll Ll Lr

Rl Rr -0.0016 Rr Rl

-0.953 -0.928 +0.922 +0.941 ppm

$n@Ne_8(-q)_{15}$ $n@Ne_8$ $n@Ne_8(+q)_{15}$

CONCLUSIONS II

- The molecular shielding of the system of Ne_8 and point charge helices is sampled by the naked spin at the center, revealing the diastereomerism in the scalar property, the chiral shift.
- Replacing Xe by a naked spin gives a clear indication of the induced diastereomerism of the Xe electrons: the diastereomeric shift is 0.9342 ppm for Xe compared to 0.0191 ppm for the naked spin.
- When the sign of the chiral potential is changed, both the sign and the magnitude of the shift changed for a naked spin. Thus, the sign of the shift between diastereomers is not uniquely related to the handedness of the diastereomeric pairs. In other words, it may not be possible to assign the individual peaks which would be observed in an NMR spectrum unequivocally to (Ll, Rr) or (Lr, Rl).

Antisymmetric components

System	ppm
$\sigma^{\mathrm{anti}}(\mathrm{Xe@Ne_8Ll_+})$	0.4126
$\sigma^{\mathrm{anti}}(\mathrm{Xe@Ne_8Lr_+})$	0.1504
$\sigma^{\mathrm{anti}}(\mathrm{n@Ne_8Ll_+})$	0.0555
$\sigma^{\mathrm{anti}}(\mathrm{n@Ne_8Lr_+})$	0.0556
$\sigma^{\mathrm{anti}}(\mathrm{n@Ne_8Ll_-})$	0.0555
$\sigma^{\mathrm{anti}}(\mathrm{n@Ne_8Lr_-})$	0.0589
$\sigma^{\mathrm{anti}}(\mathrm{n@e^-Ll})$	0.2392
$\sigma^{\mathrm{anti}}(\mathrm{n@e^-Lr})$	0.2142

Diastereomeric shifts

System	ppm
$\sigma(Xe@Ne_8Ll_+)$ $- \sigma(Xe@Ne_8Lr_+)$	-0.9342
$\sigma(n@Ne_8Ll_+)$ $- \sigma(n@Ne_8Lr_+)$	-0.0191
$\sigma(n@Ne_8Ll_-)$ $- \sigma(n@Ne_8Lr_-)$	+0.0258
$\sigma(n@e^-Ll)$ $- \sigma(n@e^-Lr)$	+0.03605

GRAND CONCLUSIONS:

Manifestation of chirality in a scalar measurement (shielding tensor):
Chirality appears explicitly if and only if the given chiral system is coupled to another chiral system (diastereomerism).

I. We looked at induced chirality and induced diastereomerism.

Replacing tethers with chiral potentials appears an adequate method of simulating diastereomerism

II. We replaced the Xe by a naked spin to examine explicitly how the Xe electrons are affected by their interaction with diastereomers:

Antisymmetric tensor element splitting is an order of magnitude larger in Xe than in the naked spin.
This is a new manifestation of diastereomerism.

IV. The odd and even character of the shielding response to a chiral potential

$V(\pm q,\mathbf{r})$ a potential at point **r** due to an outer helix of partial charges of value ±q:

$$V(\pm q, \mathbf{r}) = \pm q\, V(\mathbf{r})$$

From a right-handed helix of partial charges,

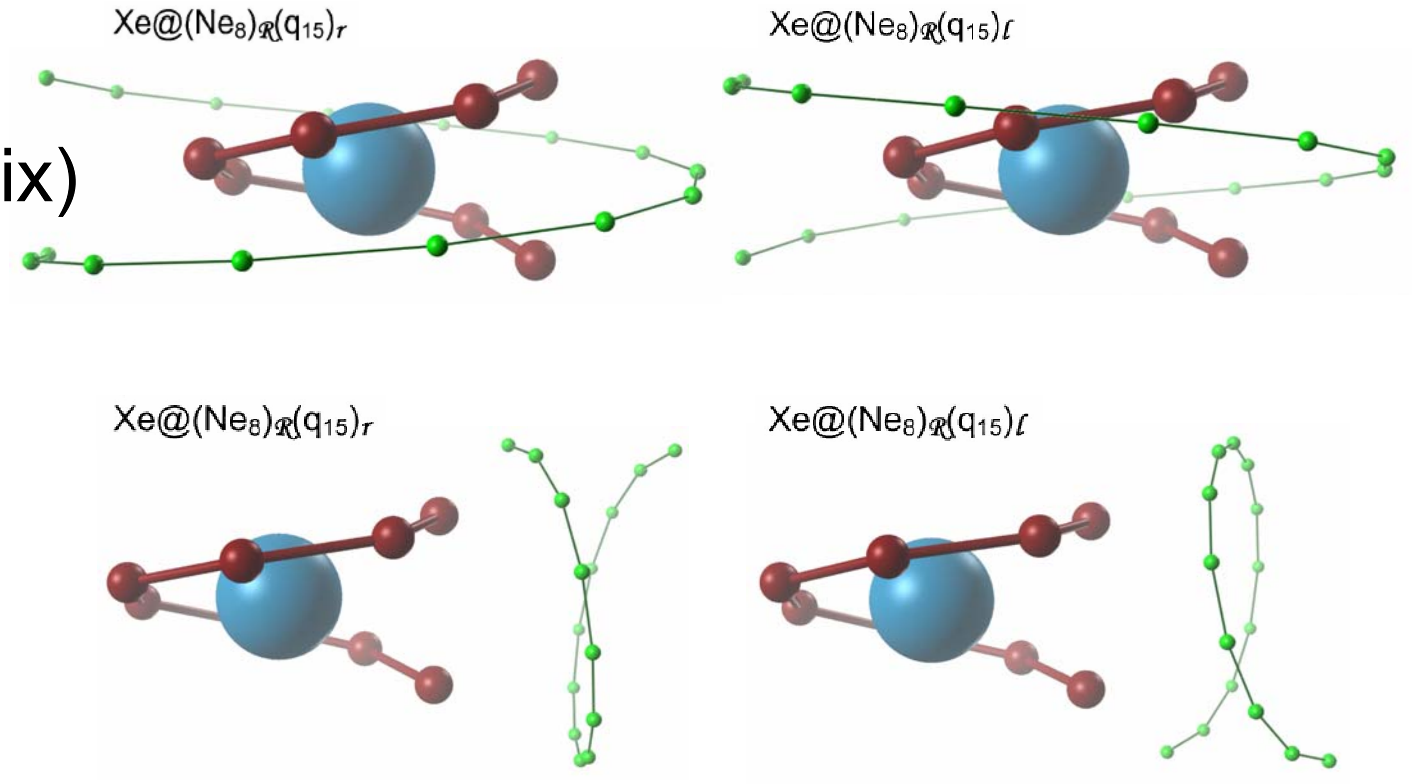
$$[V(\mathbf{r})]\ \mathit{right} \equiv V_{\mathrm{even}}(\mathbf{r}) + V_{\mathrm{odd}}(\mathbf{r})$$

From a left-handed helix of partial charges,

$$[V(\mathbf{r})]\ \ell\mathit{eft} = V_{\mathrm{even}}(\mathbf{r}) - V_{\mathrm{odd}}(\mathbf{r})$$

The odd and even character of the shielding response

in a chiral molecule (modeled by a Ne_8 helix) when subjected to a chiral potential (modeled by a helix of point charges).



For Xe in a right-handed Ne_8 helix **R** there are four unique nuclear magnetic shieldings due to *right* or *left-handed* helix of charges +q or -q:

$\sigma_{\mathbf{R}r}(+q)$, $\sigma_{\mathbf{R}r}(-q)$, $\sigma_{\mathbf{R}\ell}(+q)$, and $\sigma_{\mathbf{R}\ell}(-q)$

$$\sigma_{\mathbf{R}r}(\pm q) = \pm q(\sigma_e + \sigma_o)$$
$$+ (q^2/2!)(\sigma_{ee} + \sigma_{oo} + 2\sigma_{eo}) +$$
$$\pm (q^3/3!)(\sigma_{eee} + \sigma_{ooo} + 3\sigma_{eoo} + 3\sigma_{eeo}) +$$

. . .

$$\sigma_{\mathbf{R}\ell}(\pm q) = \pm q(\sigma_e - \sigma_o)$$
$$+ (q^2/2!)(\sigma_{ee} + \sigma_{oo} - 2\sigma_{eo}) +$$
$$\pm (q^3/3!)(\sigma_{eee} - \sigma_{ooo} + 3\sigma_{eoo} - 3\sigma_{eeo}) +$$

. . .

The derivatives of the shielding
with respect to V_{even} and V_{odd}
are denoted by subscripts e and o

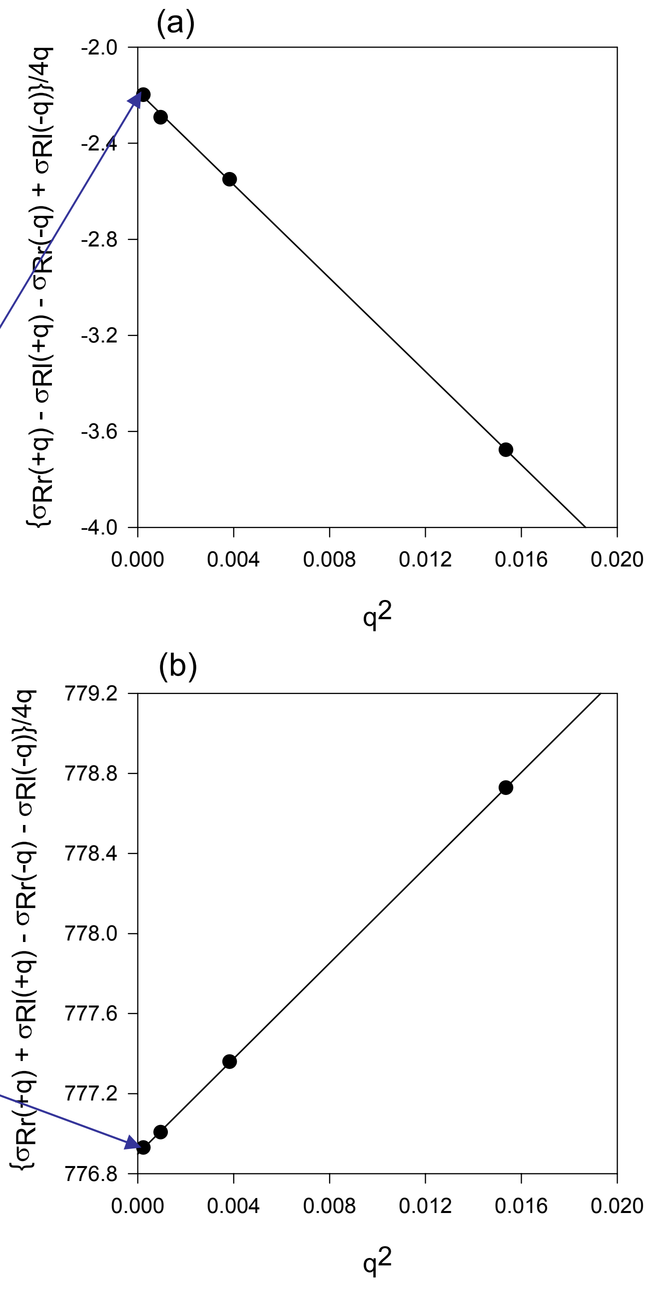
The charge dependence of the Xe shielding

provides values of the derivatives:

q^2 and q^3 terms give:

(a) The intercept is σ_o,
and the slope is
$[\sigma_{ooo} + 3\sigma_{eeo}]/3!$.

(b) The intercept is σ_e,
and the slope is
$[\sigma_{eee} + 3\sigma_{eoo}]/3!$.



The charge dependence of the Xe shielding

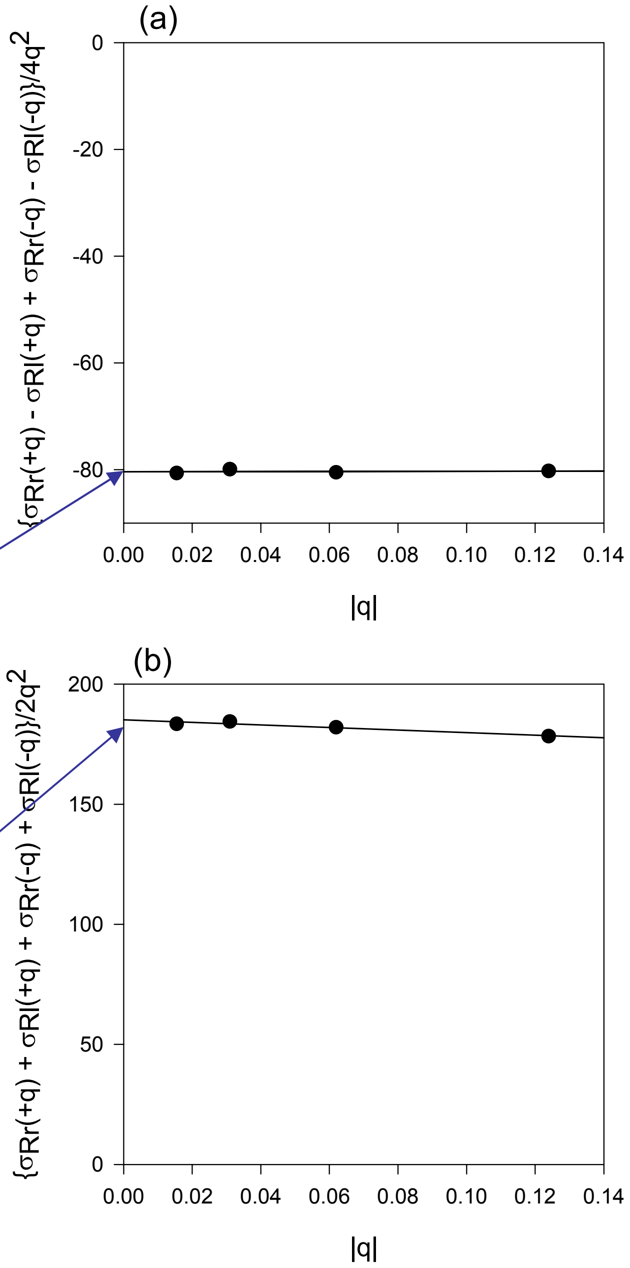
provides values of the derivatives:

In the limit q→0, the values are

(a) σ_{eo}

and

(b) $\{\sigma_{ee} + \sigma_{oo}\}$



The diastereomeric splittings are

$$\delta(\pm q) = (\pm 2q)\sigma_{o} + (q^2/2!)(\,4\sigma_{eo}) \pm (q^3/3!)2(\sigma_{ooo} + \,3\sigma_{eeo}) + \ldots$$

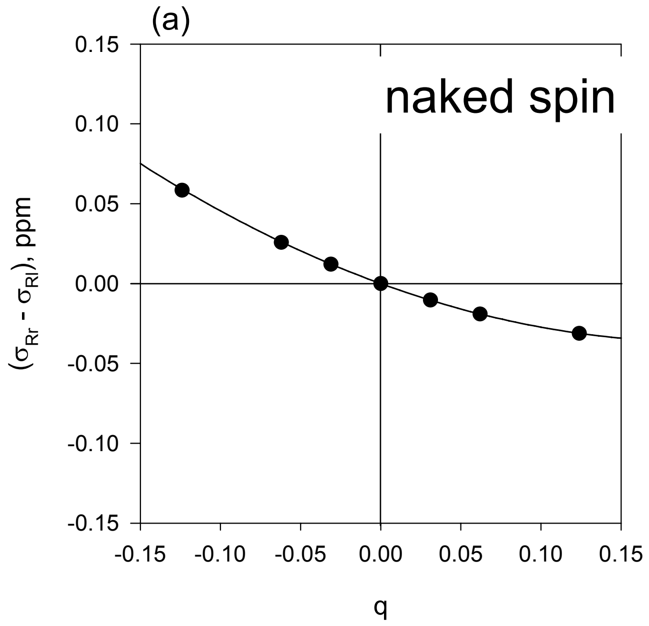
Thus,

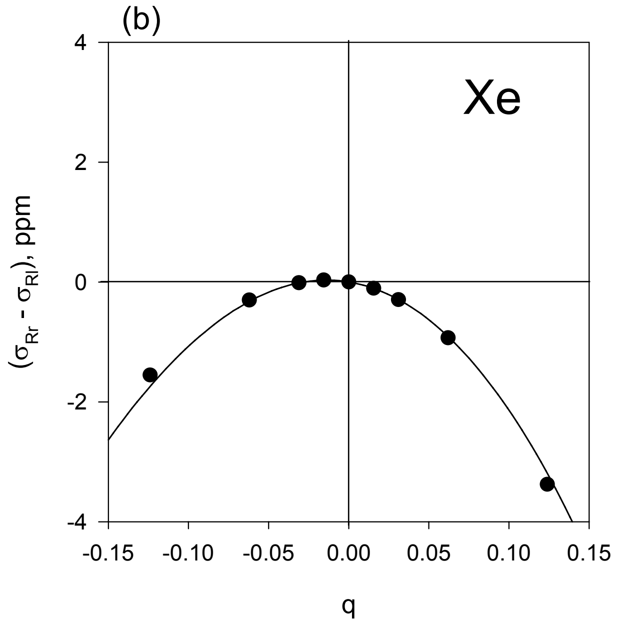
the diastereomeric splittings are a measure of odd powers of V_{odd}.

The dependence of the diastereomeric splitting on the charge

(a) for the naked spin, the sign of $\sigma_{\mathbf{R}r} - \sigma_{\mathbf{R}\ell}$ depends on the sign of the charges

(b) for Xe, the sign of $\sigma_{\mathbf{R}r} - \sigma_{\mathbf{R}\ell}$ is the same for +q or –q charges

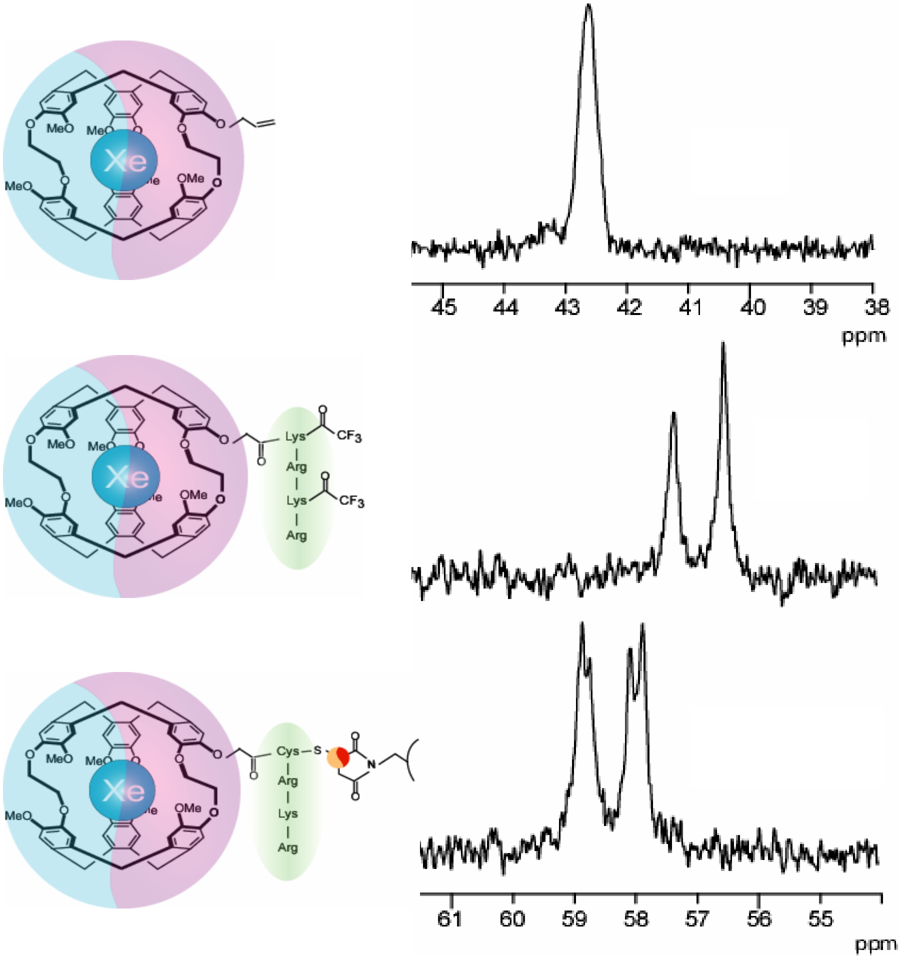




CONCLUSION IV:

- **For Xe**, although the magnitude of the splitting depends on the magnitudes of the electrostatic potential, for a given configuration of diastereomers, **the chirality of the potential alone determines the sign of the diastereomeric splitting**. In other words, unique assignment of the peaks to **R**ℓ or **R**r is possible.
- **Geometry affects the sign of the diastereomeric splitting.** For a second configuration of diastereomers, the sign of the splitting can be different, but as above, does not change with +q or -q

V. Epilogue: Xe diastereomeric shifts in the biosensor and its precursors

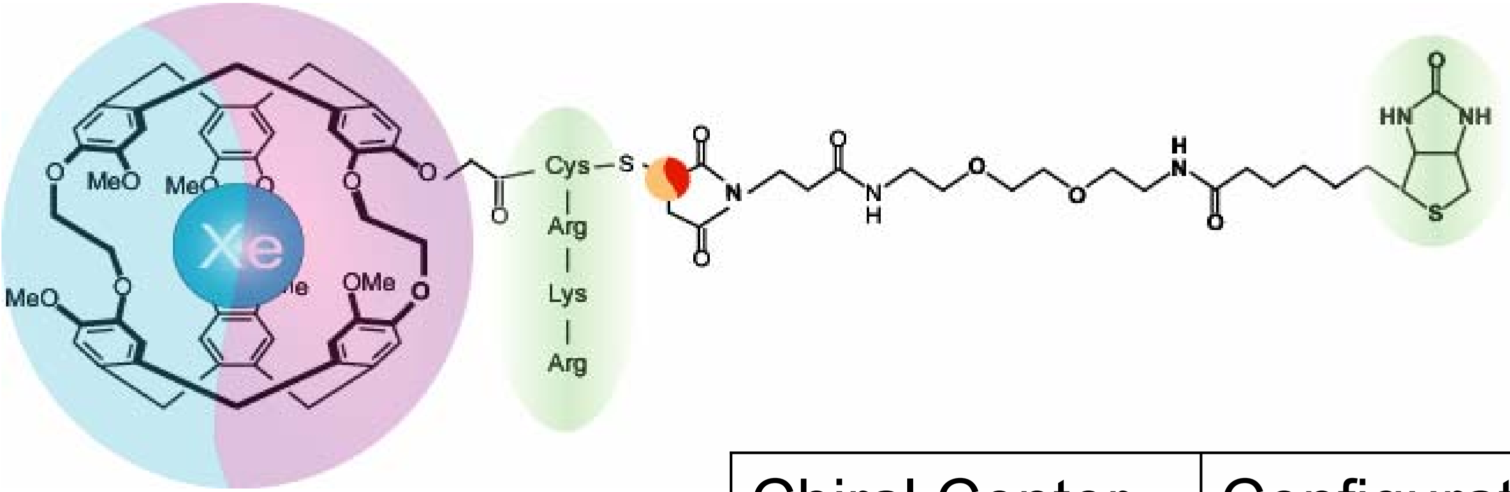


R and **L**

Rl and **L**l

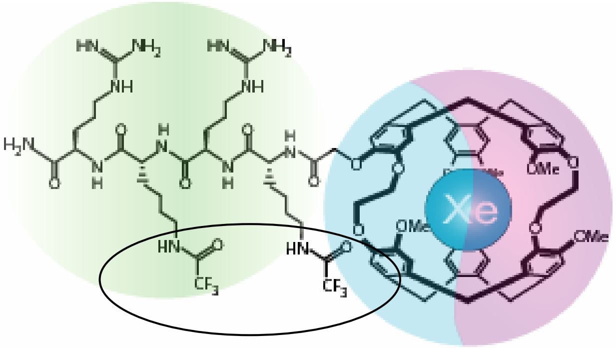
Rl*l*, **L**l*l*, **R**l*r*, and **L**l*r*

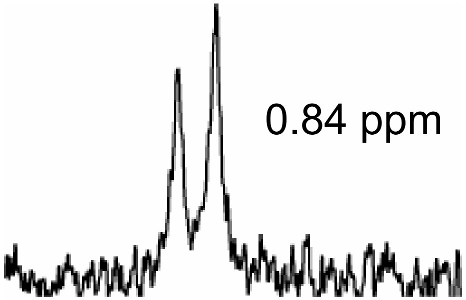
Chiral Components of the biosensor

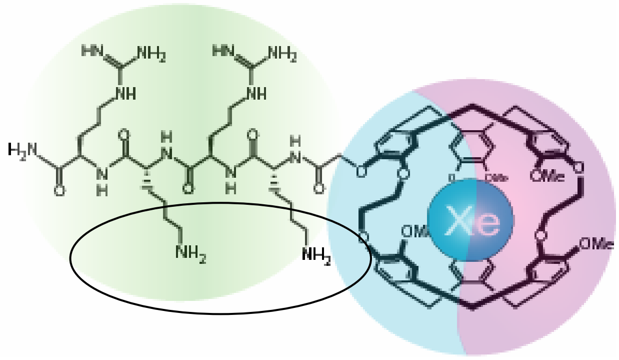


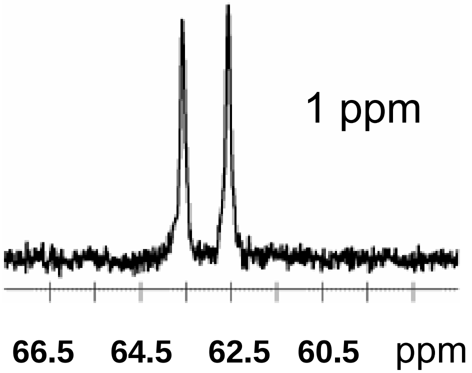
Chiral Center	Configuration			
Cage	L	L	R	R
Peptide	L	L	L	L
Asymmetric Carbon	L	R	L	R
Ligand	D	D	D	D

TFA Substitution

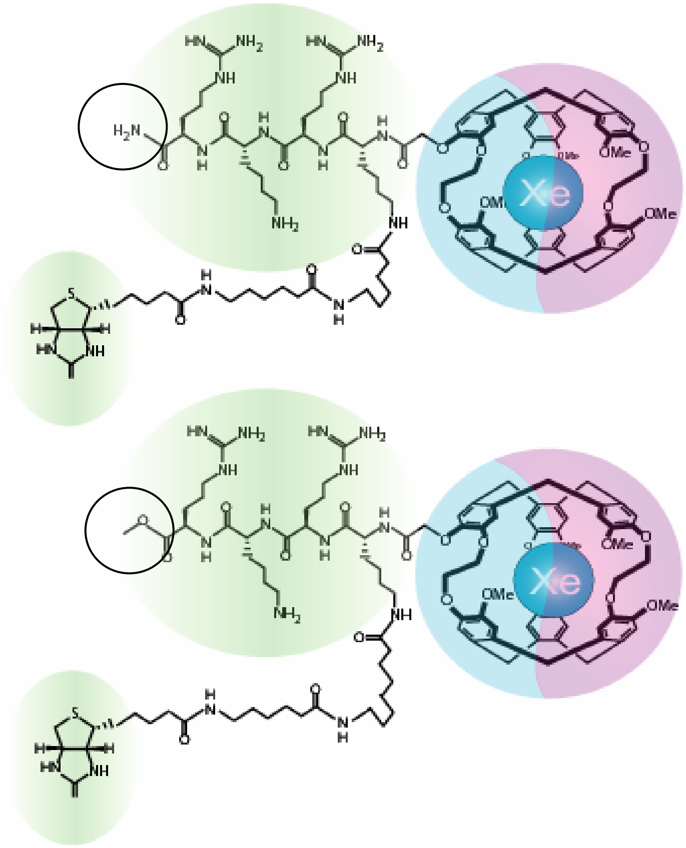


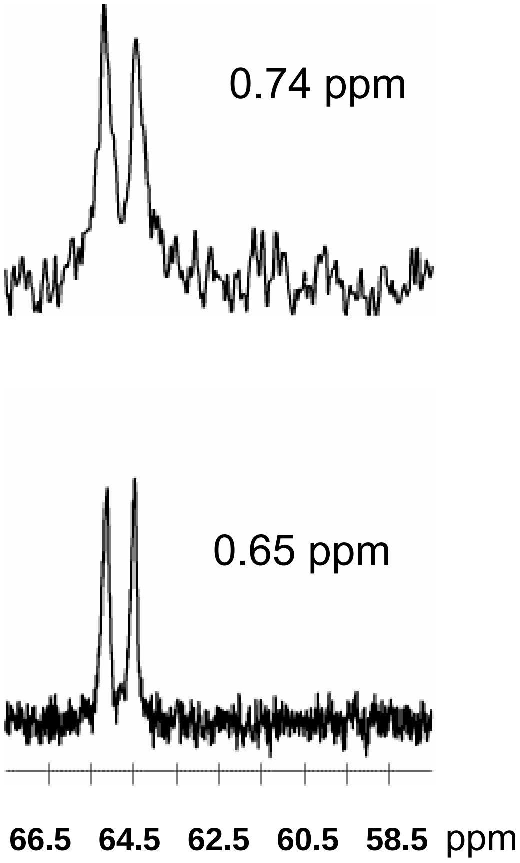

0.84 ppm



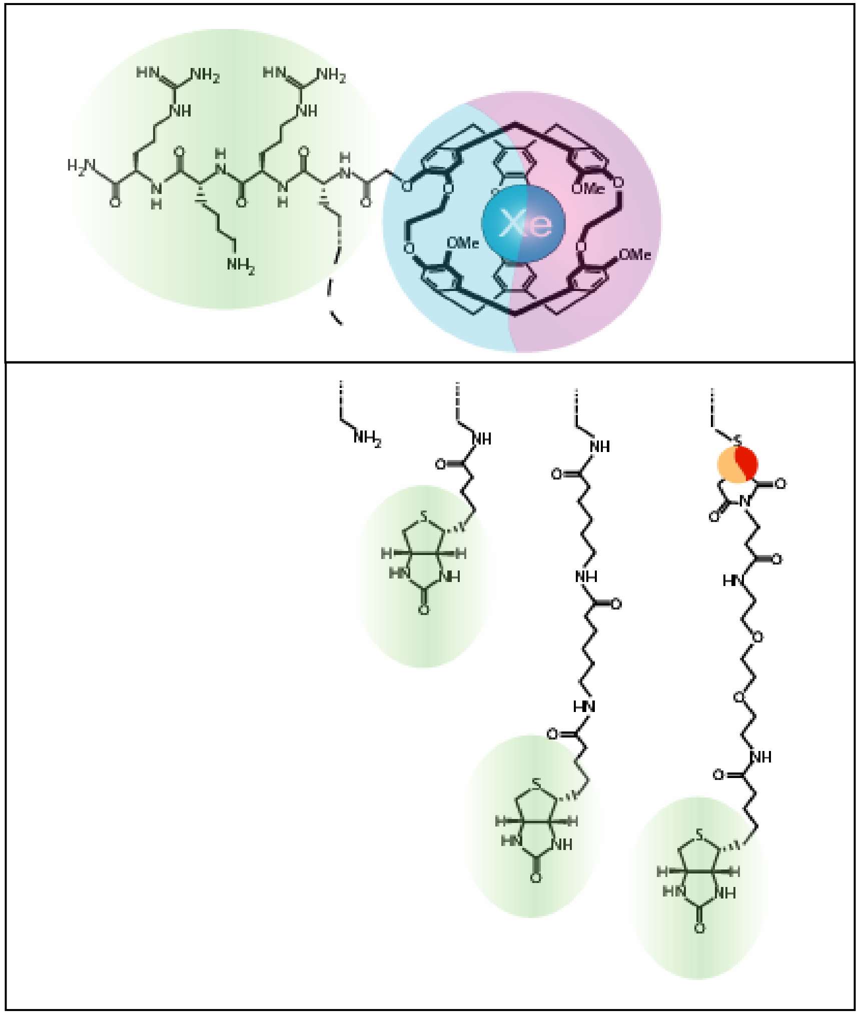

1 ppm

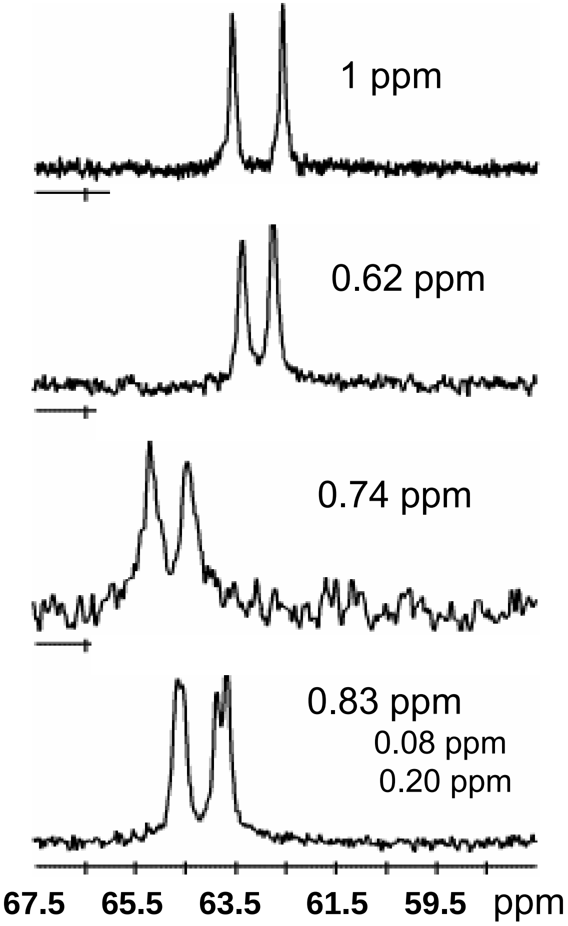
$-NH_2$ Substitution





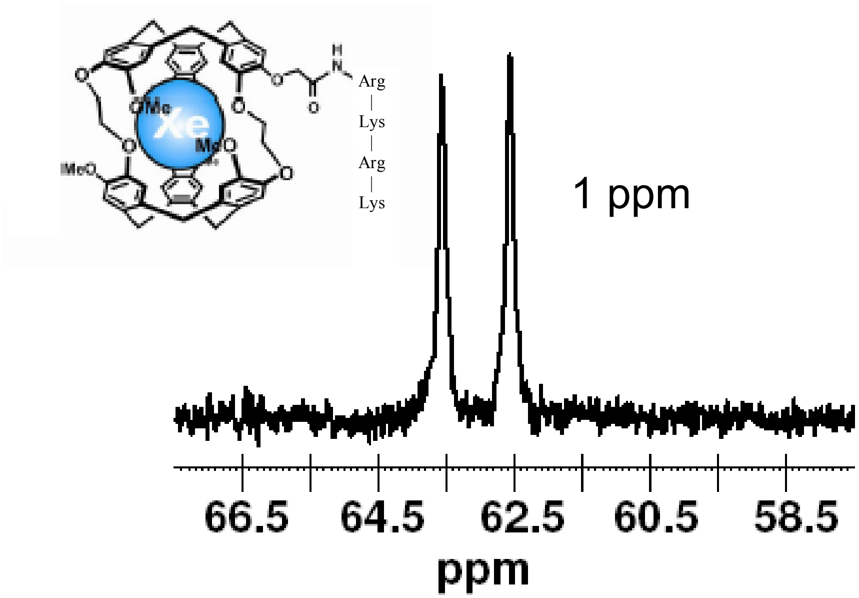
More examples:





Xe signal is split

With D_{3d} symmetry, the cryptophane-A cage is **chiral**.
When a further chiral functional group is substituted onto the cryptophane-A cage, the ^{129}Xe NMR signal from the xenon sequestered within the cage is split into two or more peaks.

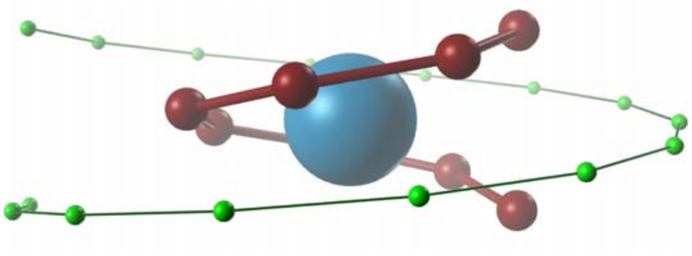


M. M. Spence, E. J. Ruiz, S. M. Rubin,T. J. Lowery, N. Winssinger, P. G. Schultz, D. E. Wemmer, A. Pines, J. Am. Chem. Soc. 126, 15287 (2004)

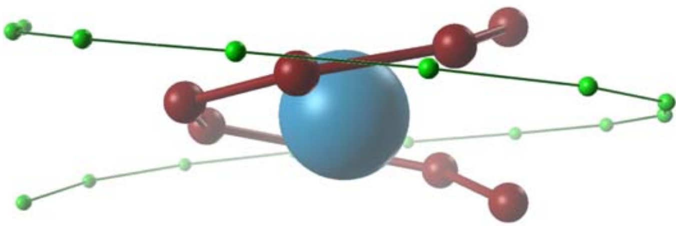
To understand diastereomeric shifts of Xe we studied model systems:

Xe in helical arrangements of atoms and partial charges at coaxial or perpendicular configurations, to establish that the chiral nature of real tethers can be modeled by differently oriented partial charges

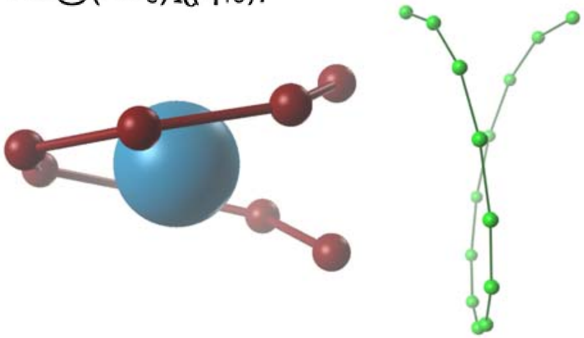
$Xe@(Ne_8)_{\mathcal{R}}(q_{15})_r$



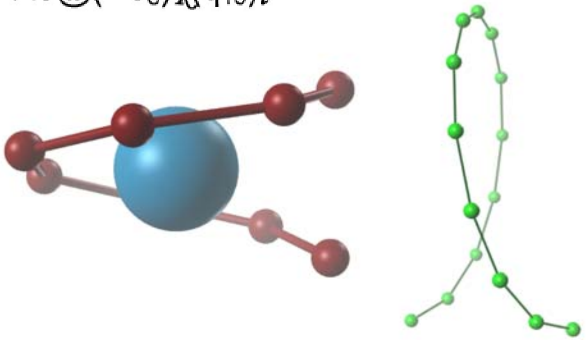
$Xe@(Ne_8)_{\mathcal{R}}(q_{15})_\ell$



$Xe@(Ne_8)_{\mathcal{R}}(q_{15})_r$

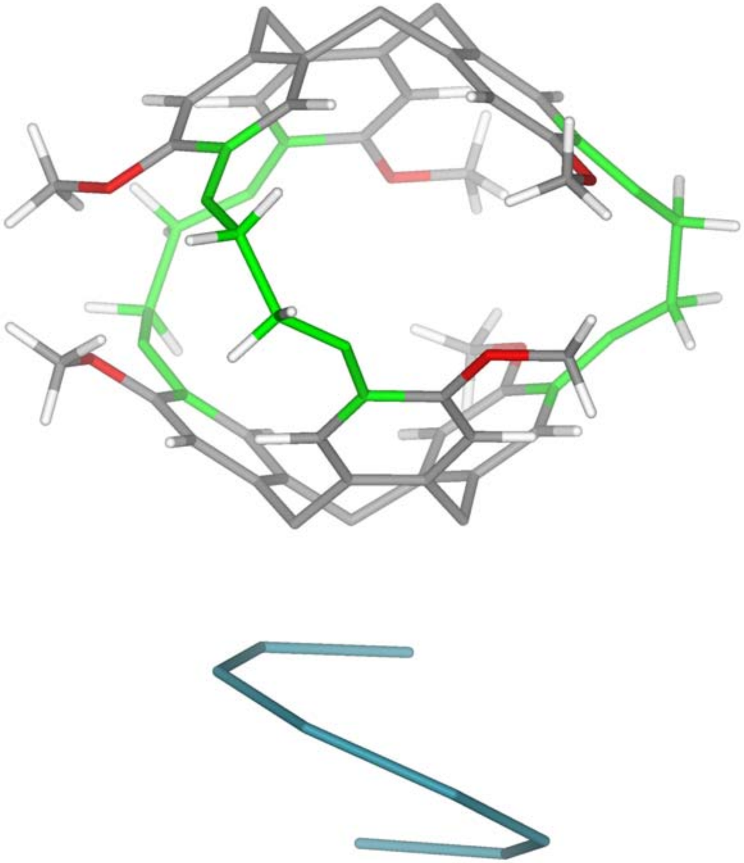


$Xe@(Ne_8)_{\mathcal{R}}(q_{15})_\ell$



The MoMo(-) enantiomer of the cryptophane-A cage.

The ***L*** label used for this cage is consistent with the ***L*** label for the left-handed helix.



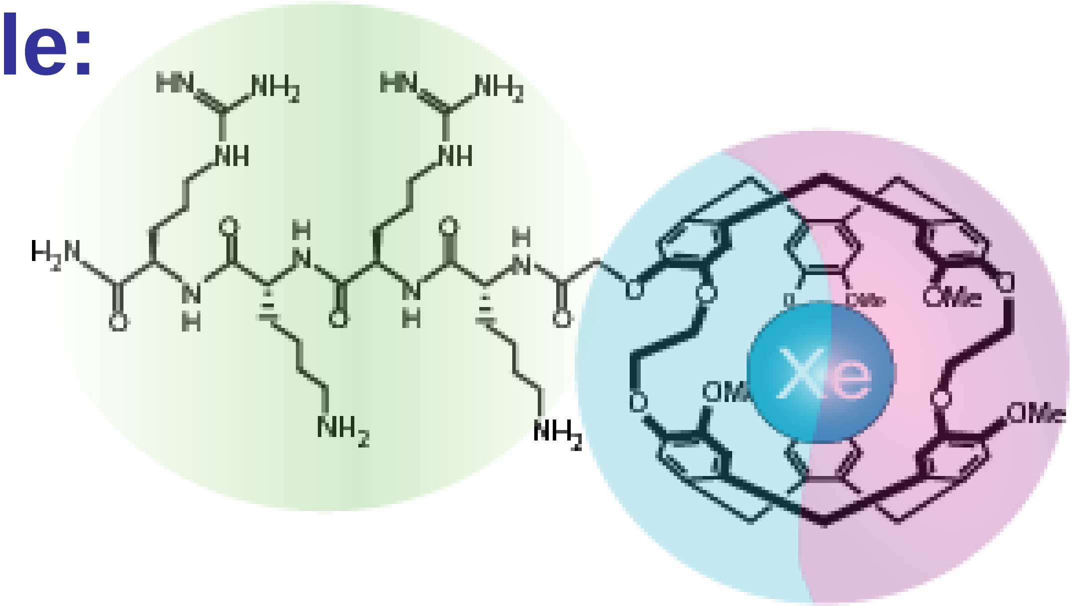
Diastereomerism of functionalized cages

chiral components		diastereomers	
cage	amino acids	configuration	**same σ** ⊙
R	***l***	***Rl***	***Lr***
L	***l***	***Ll***	***Rr***

⊙**Nuclear shieldings are related by symmetry**

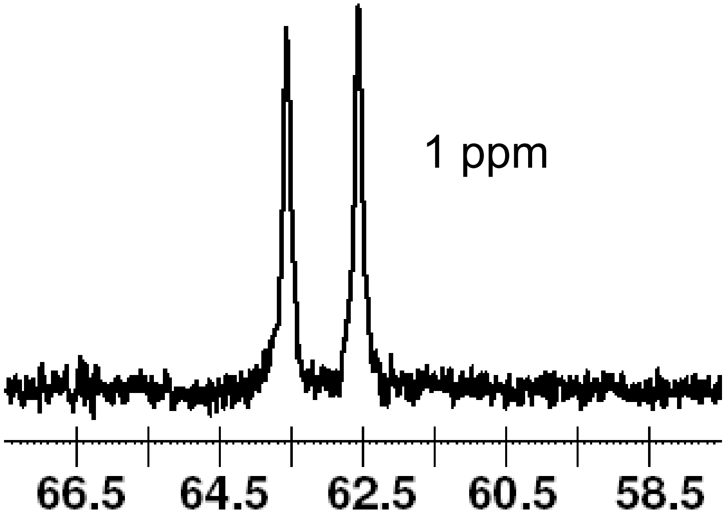
$\sigma(Rr) \equiv \sigma(Ll)$ and $\sigma(Rl) \equiv \sigma(Lr)$

Choose one example:

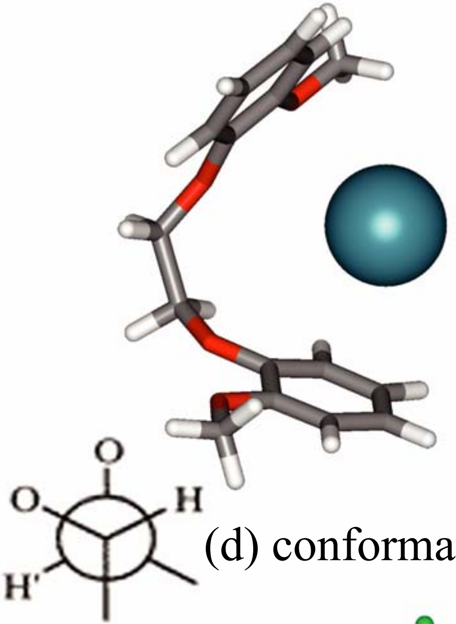


Experiment

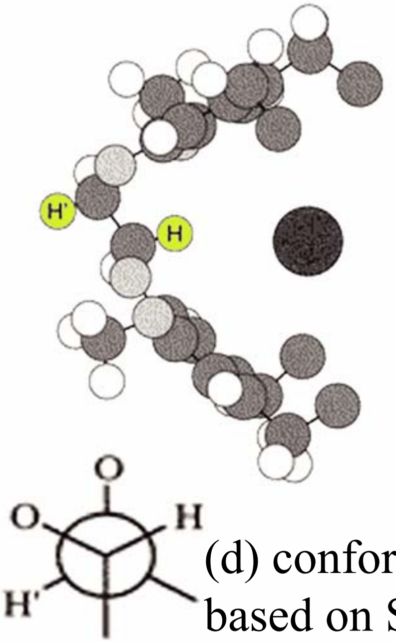
^{129}Xe NMR spectrum of Xe in a functionalized cryptophane-A cage



The average structure of Xe@cryptoA to be used for quantum calculations

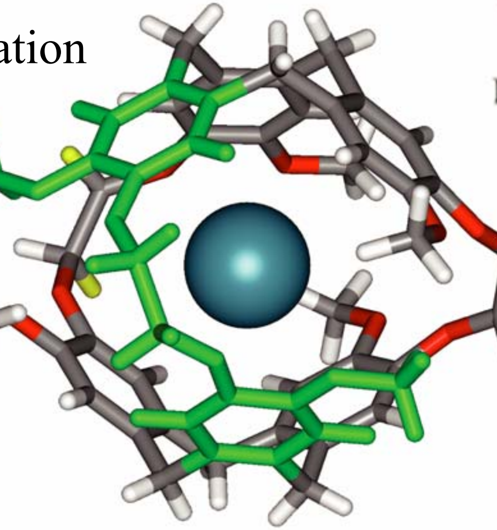


(d) conformation



(d) conformation
based on SPINOE

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



Minimum energy structure arrived at is completely consistent with SPINOE experiments

D. N. Sears, C. J. Jameson,
J. Chem. Phys. 119, 12231 (2003)

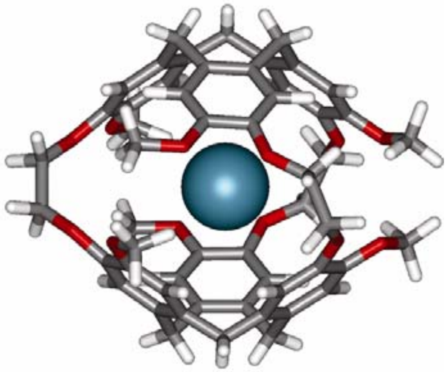
MOLECULAR DYNAMICS:

Molecular dynamics of cage with ***l*** (or ***r***) tether within a solvent box finds the equilibrium arrangement of the tether atoms relative to the cage for each member of the diastereomeric pair.

This is followed by ➦

➦ QUANTUM MECHANICAL CALCULATIONS of Xe SHIELDING

All these nuclei and electrons are included in the QM calculations of Xe shielding:

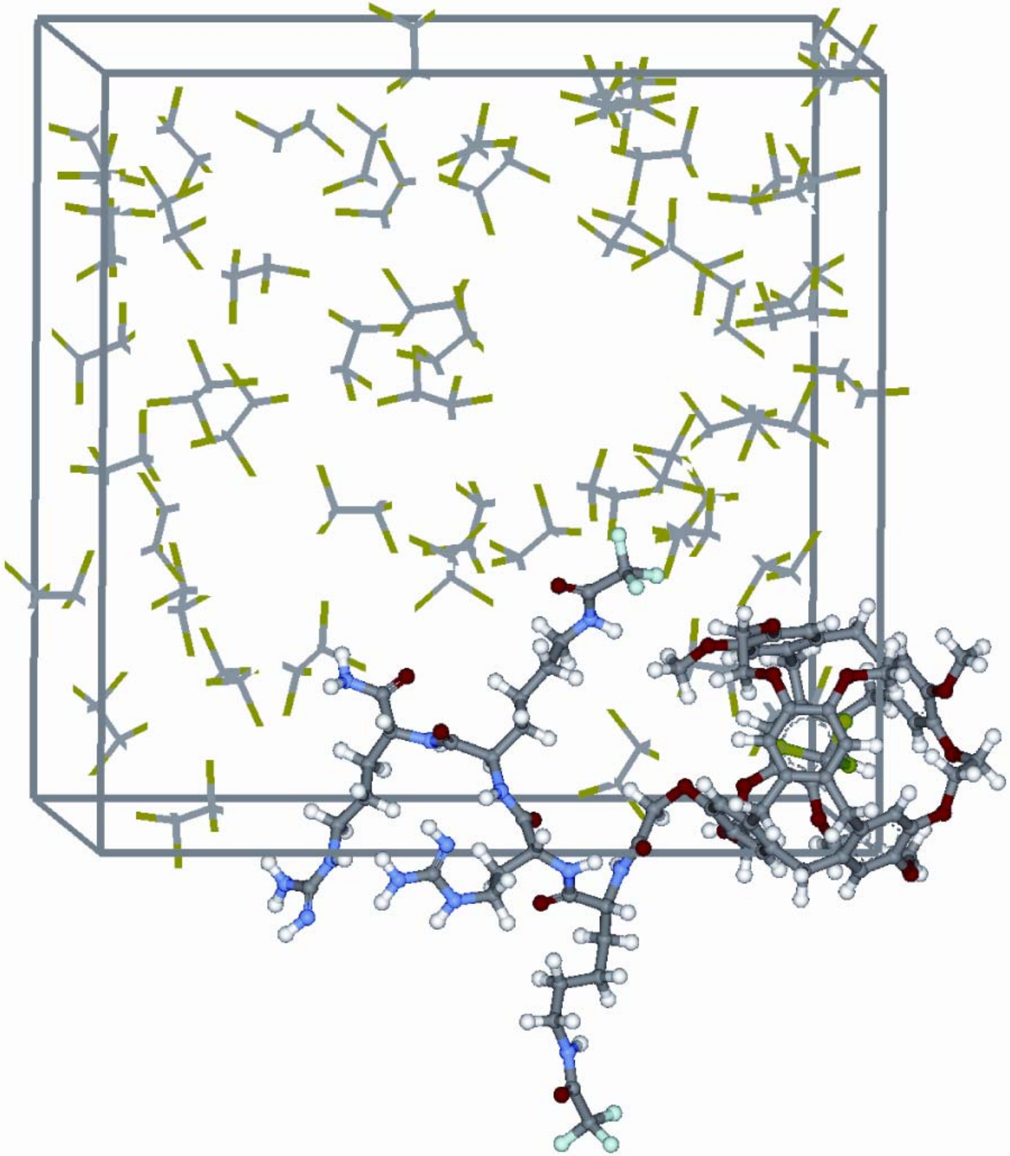


The ***l*** or ***r*** tether is included as a collection of point charges located at the equilibrium positions of the tether atoms.

MOLECULAR DYNAMICS:

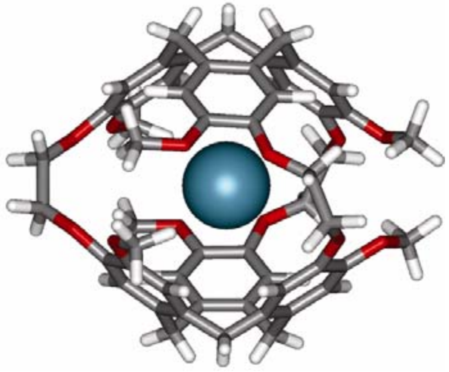
Molecular dynamics of cage with ***l*** (or ***r***) tether within a solvent box finds the equilibrium arrangement of the tether atoms relative to the cage for each member of the diastereomeric pair.

This is followed by

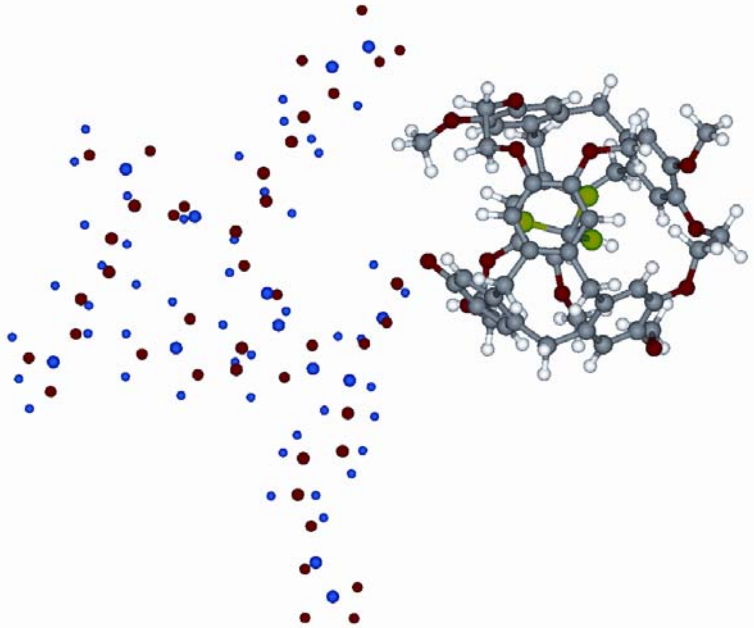


QUANTUM MECHANICAL CALCULATIONS of Xe SHIELDING

These nuclei and electrons are included in the QM calculations of Xe shielding:

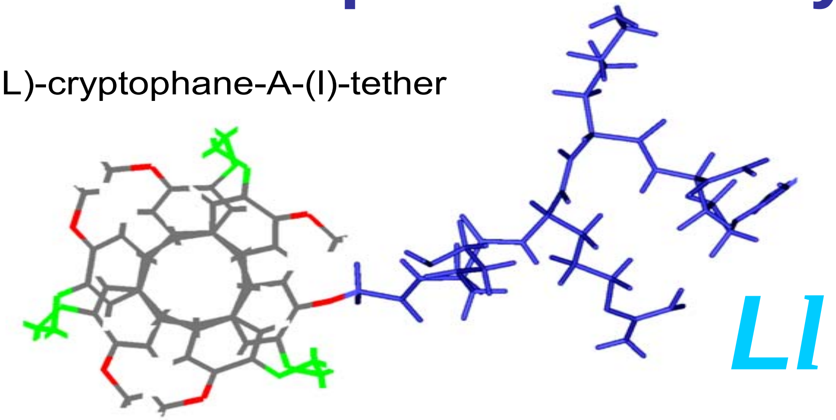


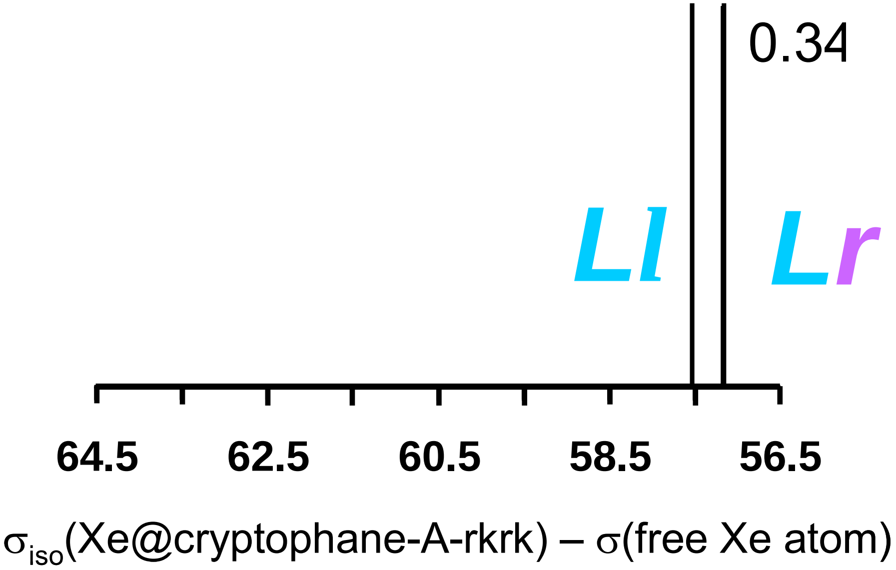
The *l* or *r* tether is included as a collection of point charges located at the equilibrium positions of the tether atoms:

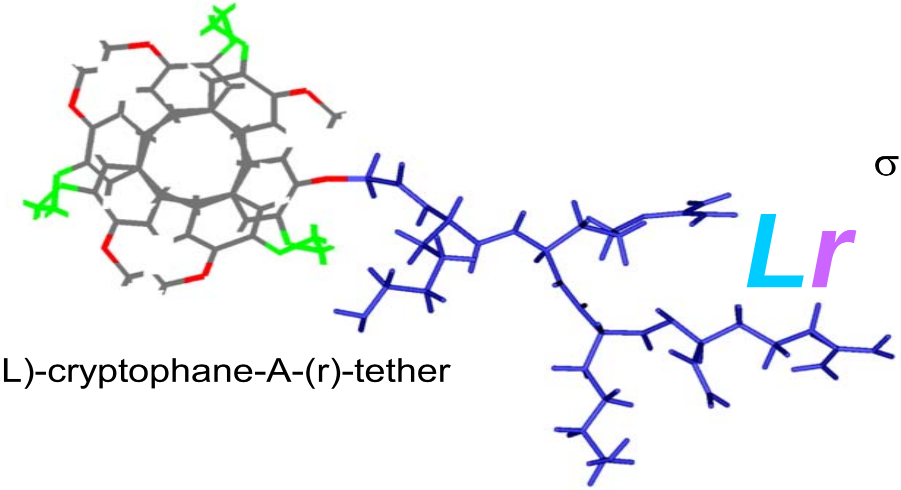


Quantum mechanical Xe shieldings for two spatial configurations of the amino acid tether with respect to the cryptophane-A cage

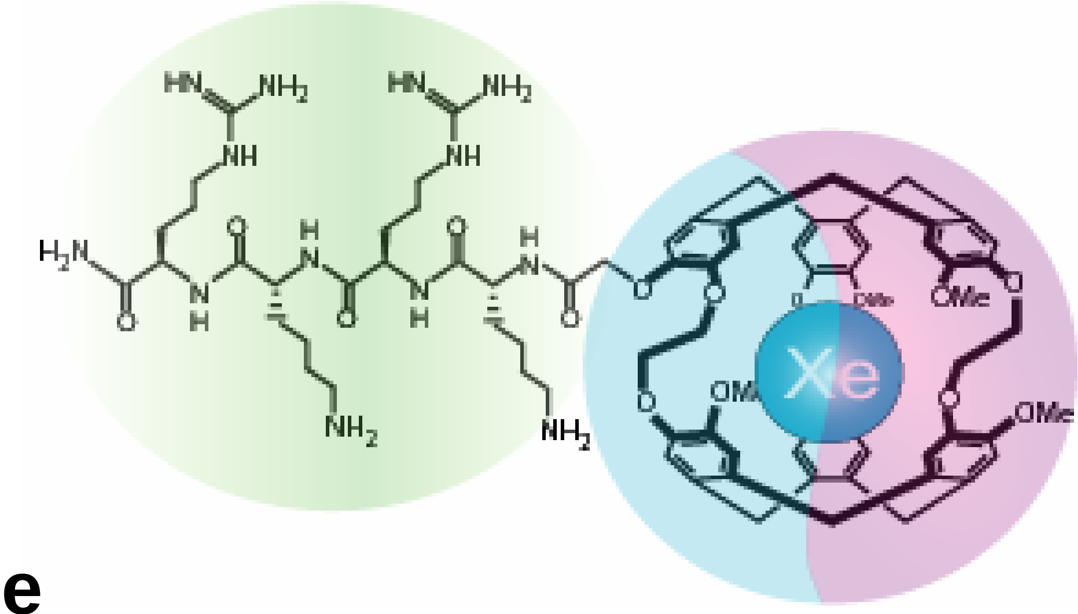
(L)-cryptophane-A-(l)-tether



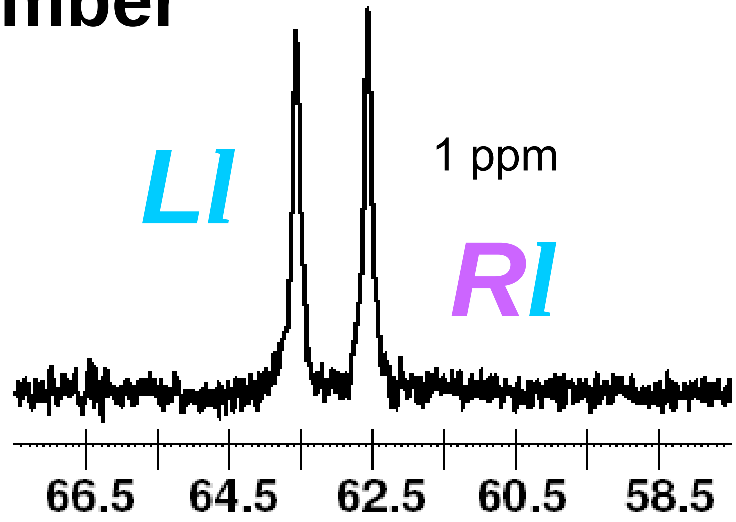




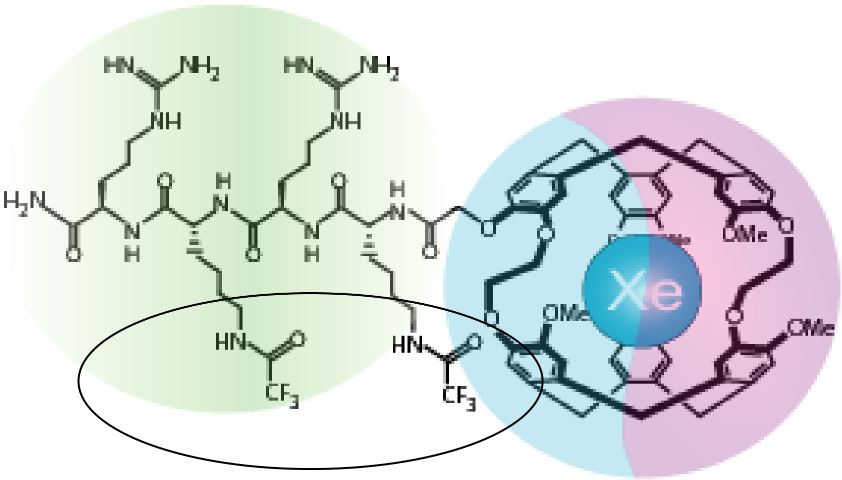
(L)-cryptophane-A-(r)-tether



Now we can assign the experimentally observed Xe signals to the specific member of the diastereomeric set

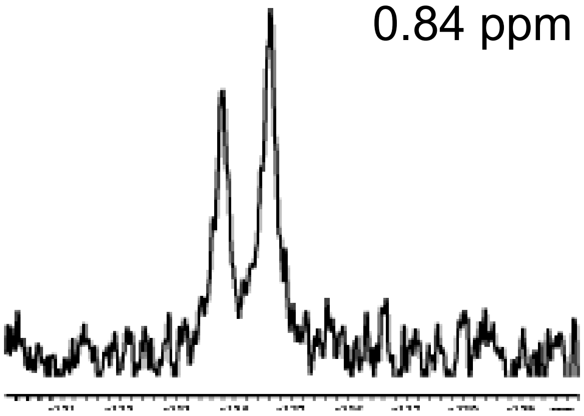


Choose a second example:



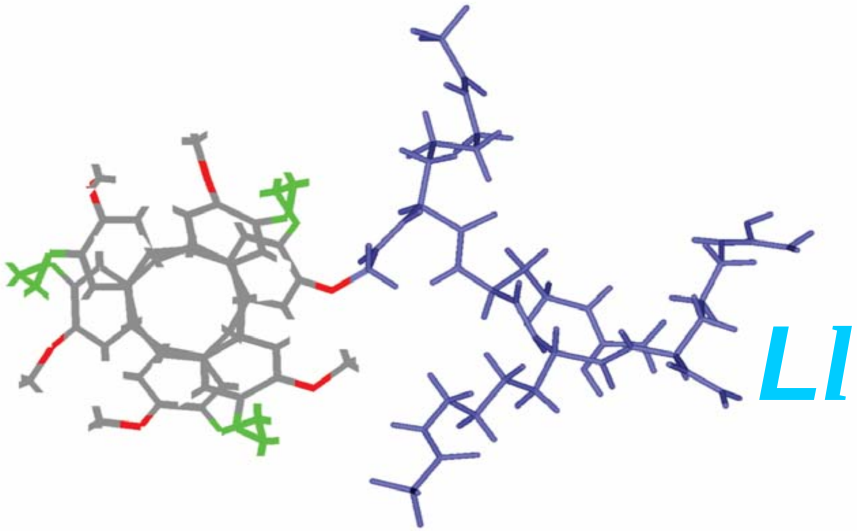
Experiment

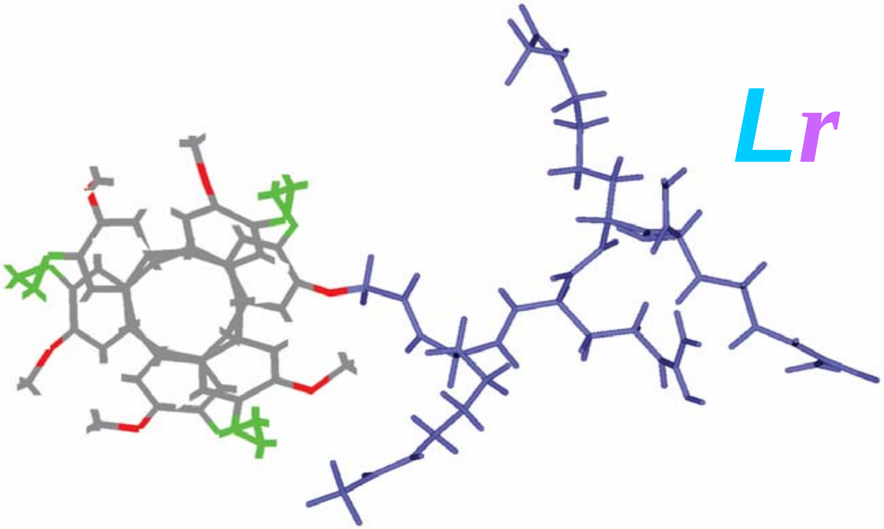
^{129}Xe NMR spectrum of Xe in a functionalized cryptophane-A cage



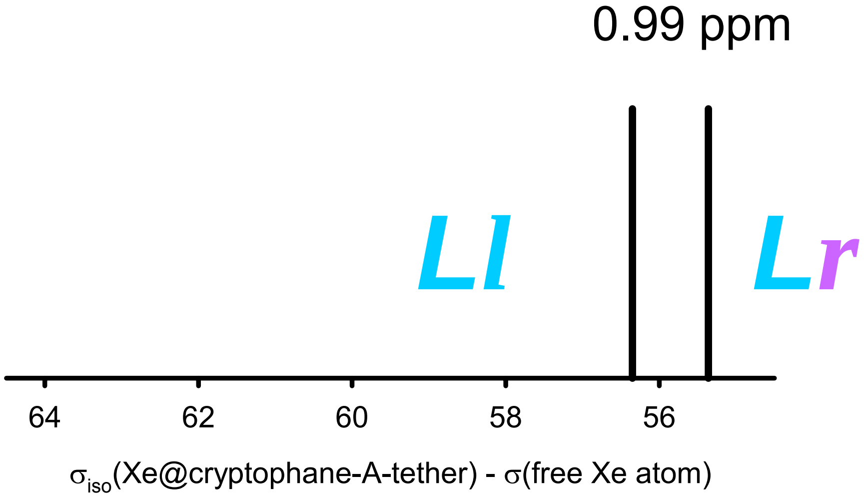
Quantum mechanical Xe shieldings for two spatial configurations of the amino acid tether

(L)-cryptophane-A-(l)-tether





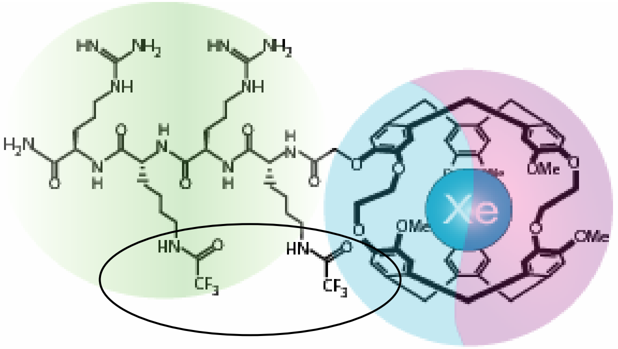
(L)-cryptophane-A-(r)-tether

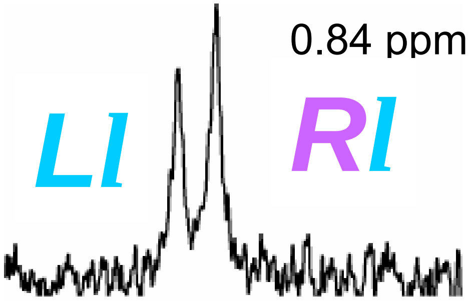


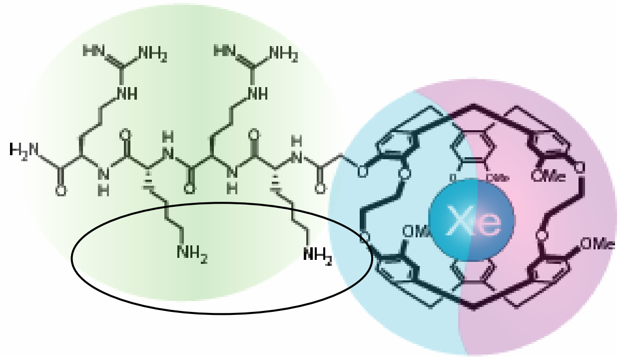
Uniqueness of this assignment is based on systematic studies of the fundamental relations between chirality and the shielding tensor.

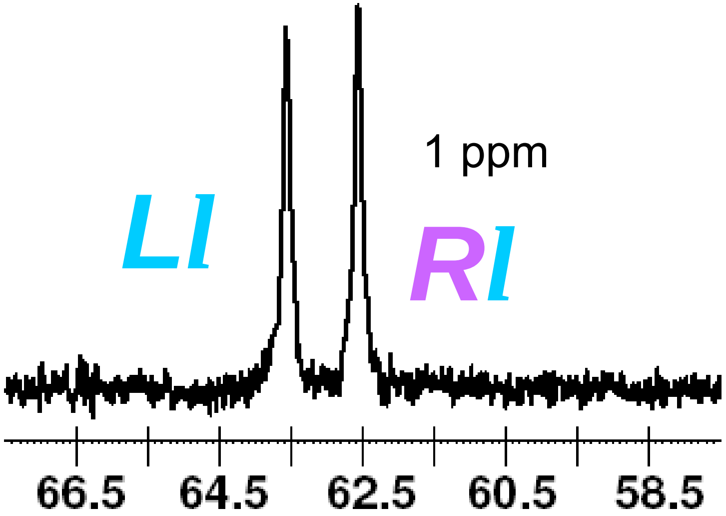
D. N. Sears, C. J. Jameson, R. A. Harris,
J. Chem. Phys, 119, 2685-2701, 120, 3277 (2004)

Now we can assign the experimentally observed Xe signals to the specific member of the diastereomeric set

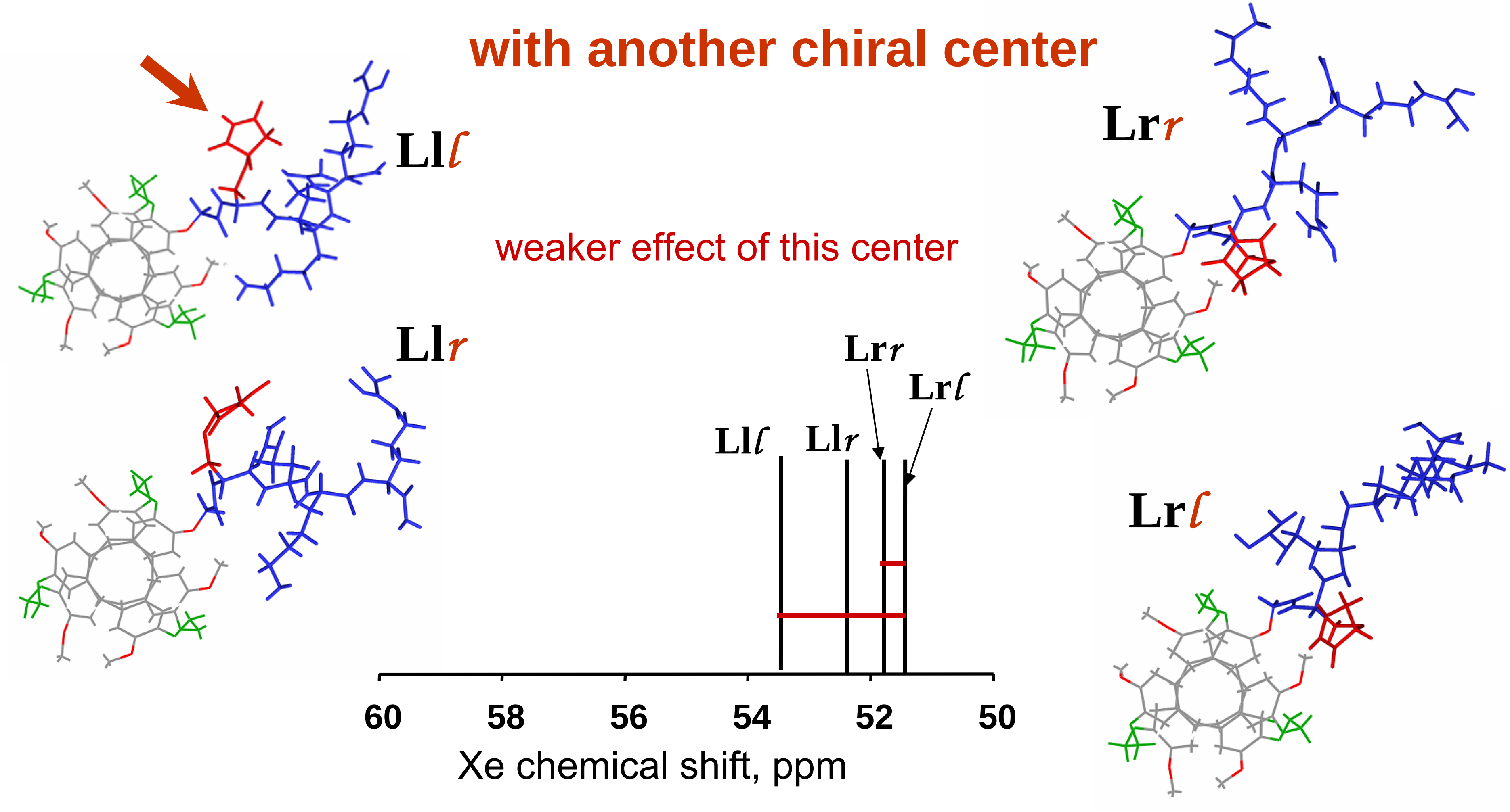








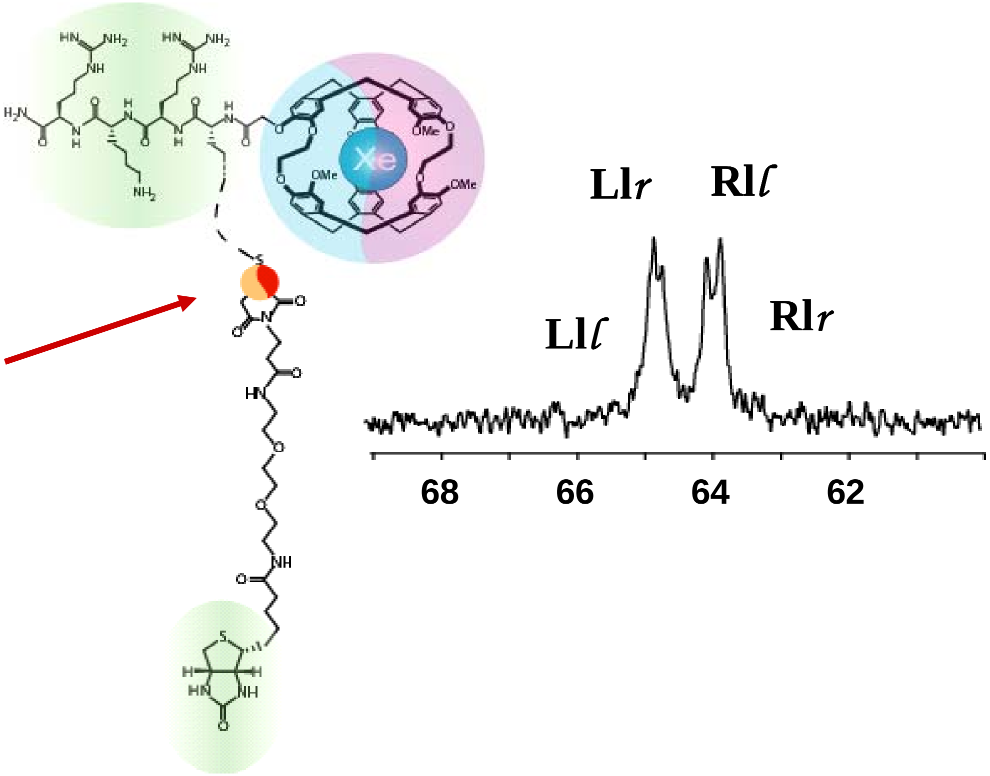
with another chiral center



weaker effect of this center

Quantum mechanical Xe shieldings for four spatial configurations of the substituent with respect to the cryptophane-A cage

Now we can assign the experimentally observed Xe signals to the specific member of the diastereomeric set



farther chiral center

CONCLUSIONS

- Xe embedded in a given chiral molecule is remarkably sensitive to the presence of further chiral systems.
- The discrimination is distinct and easily observed: Xe signals in members of diastereomeric sets are split by as much as 1 ppm
- Quantum mechanical calculations provide the assignments that could otherwise be obtained only by using enantiotopically pure cryptophane cages.

ACKNOWLEDGMENTS

Chirality:
Robert A. Harris

Calculations:
Devin N. Sears

Experiments:
E. Janette Ruiz

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