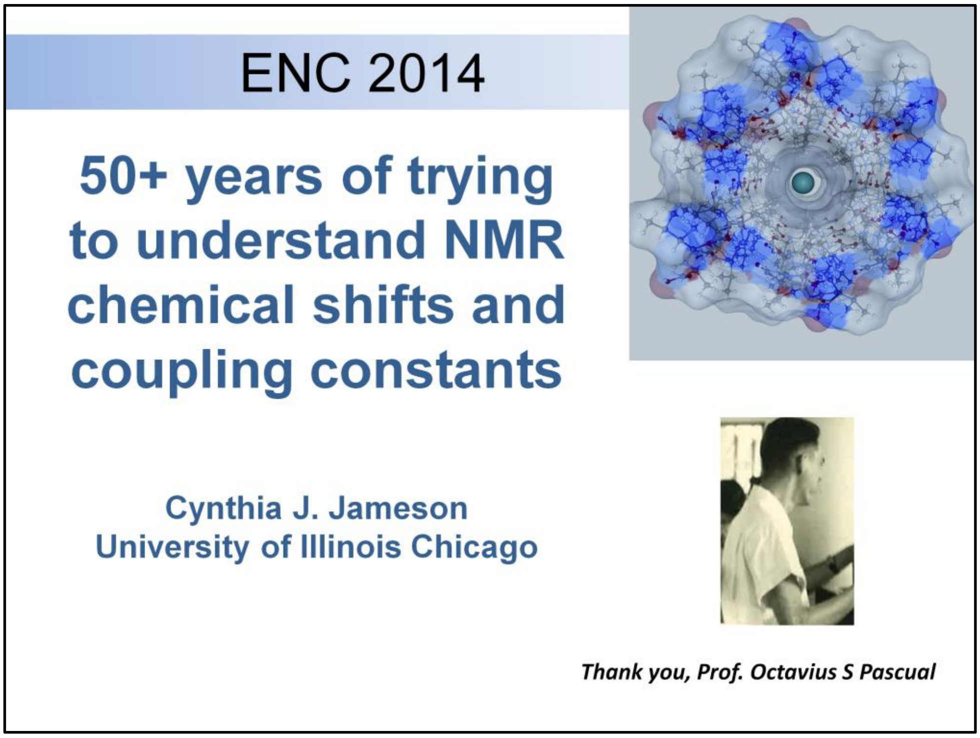


ENC 2014

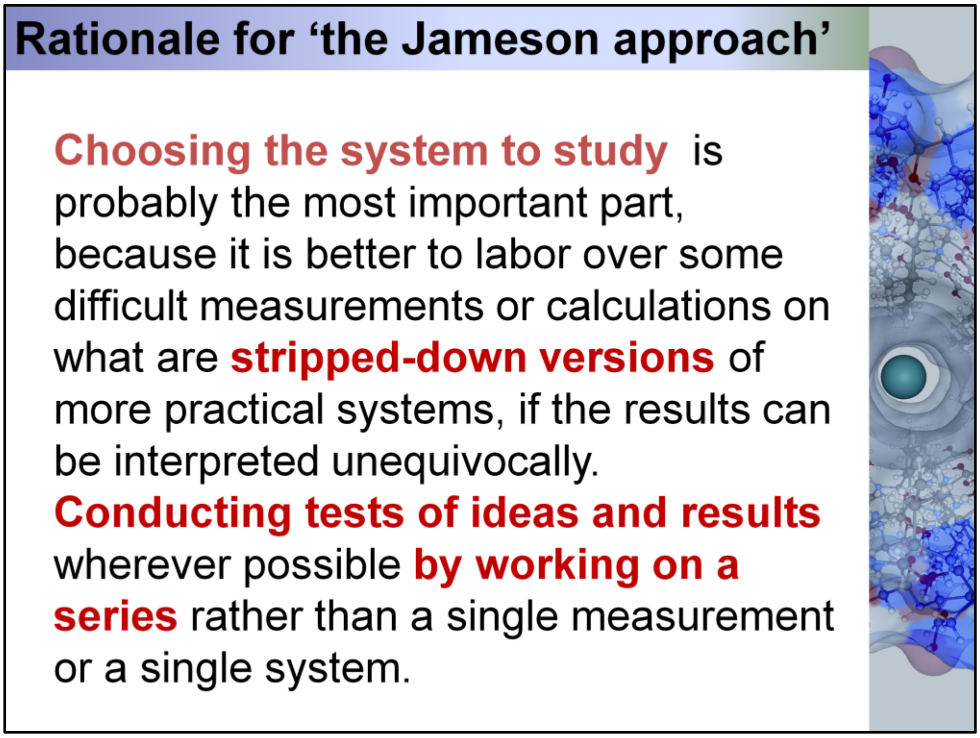
50+ years of trying to understand NMR chemical shifts and coupling constants

Cynthia J. Jameson
University of Illinois Chicago

Thank you, Prof. Octavius S Pascual

First I would like to thank Tatyana Polenova and the organizers of the ENC for inviting me to give this talk.
One of the reasons I got into the field of nmr was this guy, my undergrad prof Octavius Pascual at the University of the Philippines who had just got back from a Ph.D. in the US in 1955 and told me about many wondrous things, but in particular he said, there is a new spectroscopy called nuclear magnetic resonance and it is very powerful and will change the way we do chemistry.

In preparing this talk, looking back on a career lifetime, I asked myself, what drives me? We are extremely lucky individuals: as researchers we get to choose **wha**t we do, **how** we do it, and **what objectives we define for ourselves for the systems we work on**. I guess I was hooked on NMR parameters from the very beginning: chemical shifts, coupling constants, spin lattice relaxation. I didn't start out by stating my philosophy, but it turns out that I liked to do things a certain way and liked Physical Chemistry for that reason. So let me make my excuses for my way of doing things.

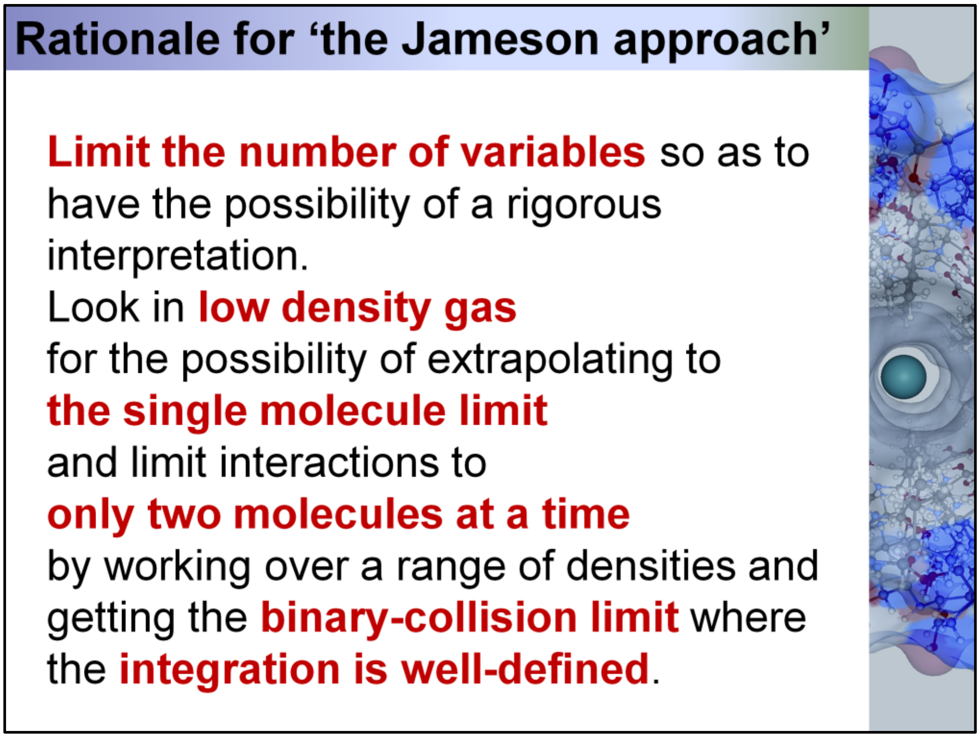


Rationale for ‘the Jameson approach’

Choosing the system to study is probably the most important part, because it is better to labor over some difficult measurements or calculations on what are **stripped-down versions** of more practical systems, if the results can be interpreted unequivocally.

Conducting tests of ideas and results wherever possible **by working on a series** rather than a single measurement or a single system.

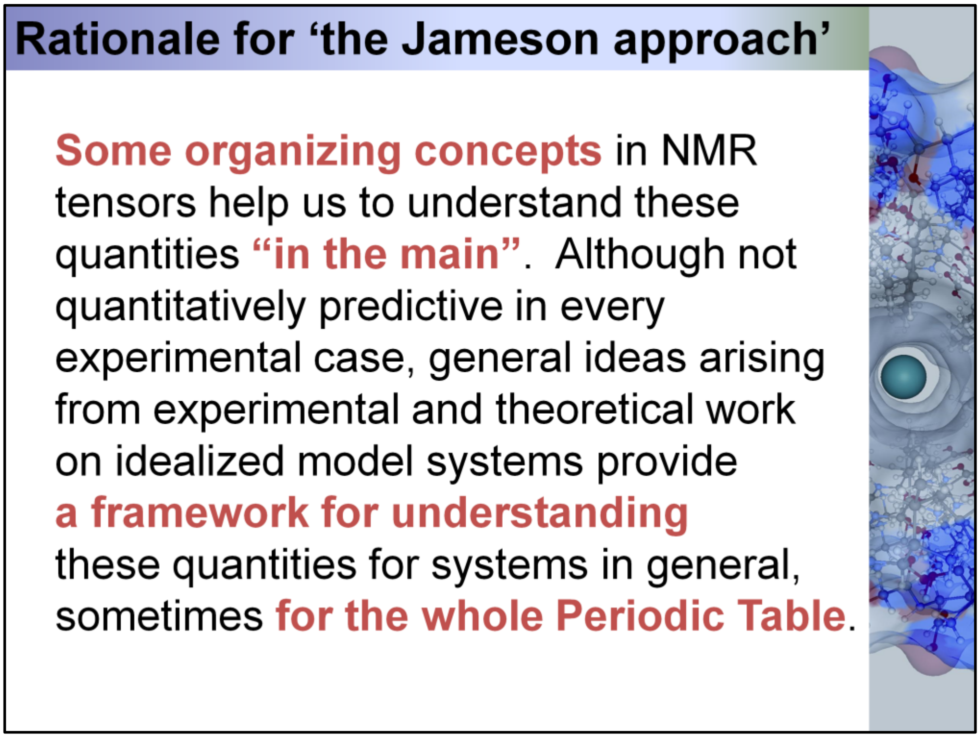
The model system may not be interesting as a practical system (real life) but a correct interpretation of a model system can be extrapolated to more complex systems by introducing additional variables one at a time, rather than studying a practical system with an unknown number of variables conflated into the measured quantity.



Rationale for ‘the Jameson approach’

Limit the number of variables so as to have the possibility of a rigorous interpretation.
Look in **low density gas**
for the possibility of extrapolating to
the single molecule limit
and limit interactions to
only two molecules at a time
by working over a range of densities and getting the **binary-collision limit** where the **integration is well-defined**.

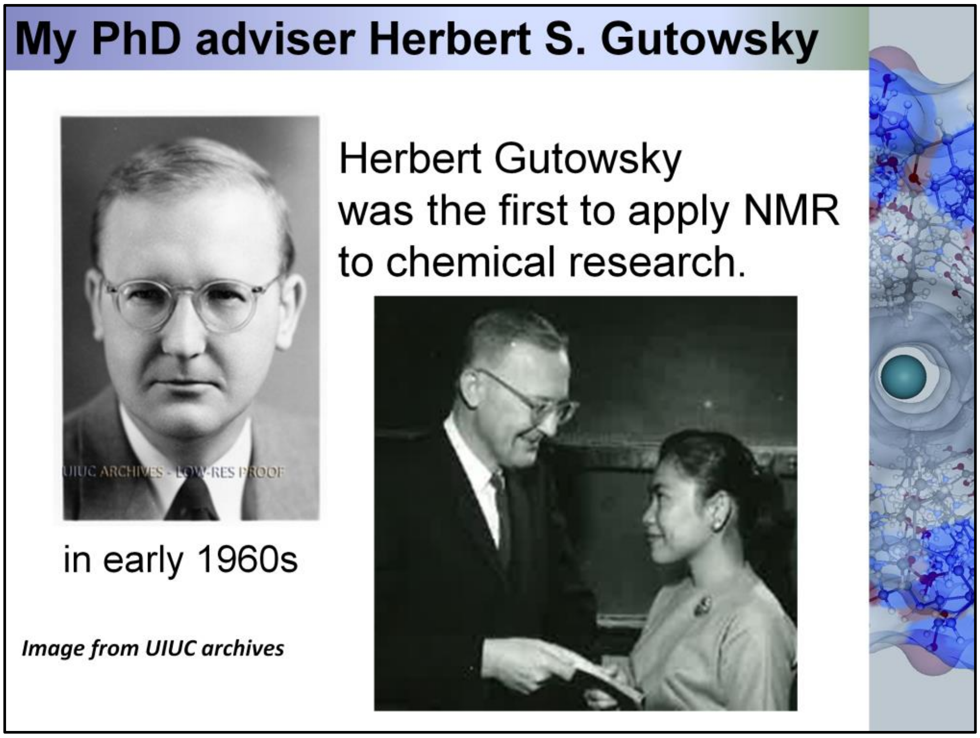
For decades Nancy True and our lab were the only ones doing gas phase NMR.



Rationale for ‘the Jameson approach’

Some organizing concepts in NMR tensors help us to understand these quantities **“in the main”**. Although not quantitatively predictive in every experimental case, general ideas arising from experimental and theoretical work on idealized model systems provide **a framework for understanding** these quantities for systems in general, sometimes **for the whole Periodic Table**.

I was always interested in getting some understanding that applies in general, otherwise how would you know that you have the right explanation, if it may apply only to one system.



My PhD adviser Herbert S. Gutowsky

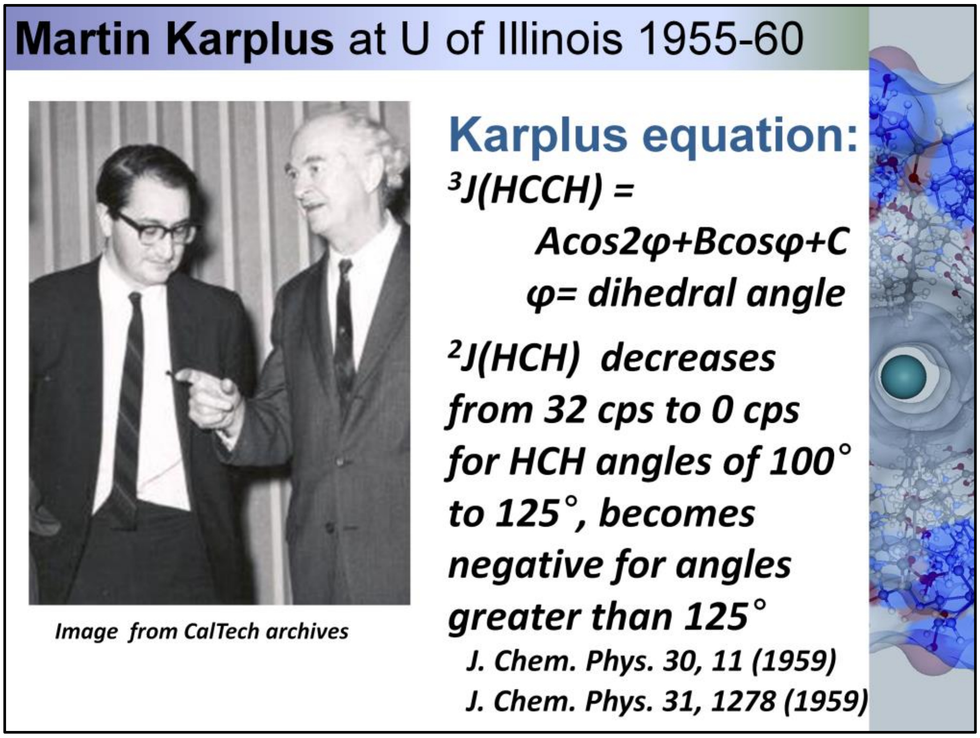
Herbert Gutowsky
was the first to apply NMR
to chemical research.

in early 1960s

Image from UIUC archives

Herb Gutowsky was the first to apply the nuclear magnetic resonance method to chemical research. His experimental and theoretical work on the chemical shift effect and its relation to molecular structure has provided the chemist with working tools to study molecular conformation and molecular interactions in solutions. Gutowsky´s pioneering work on the spin-spin coupling effect developed this phenomenon into a 'finger print' method for the identification and characterization of organic compounds. He was also the first to observe the effect of dynamic processes on the lineshape of high resolution nuclear magnetic resonance spectra, and exploited it for the studies of hindered rotation in molecules.

So let me take you along my journey as I grew up from being a fresh BS in Chemistry from the University of the Philippines, with the hope that I may leave you with some understanding of chemical shifts and coupling constants.



Martin Karplus at U of Illinois 1955-60

Karplus equation:

$^3J(HCCH) = A\cos 2\varphi + B\cos\varphi + C$

φ= dihedral angle

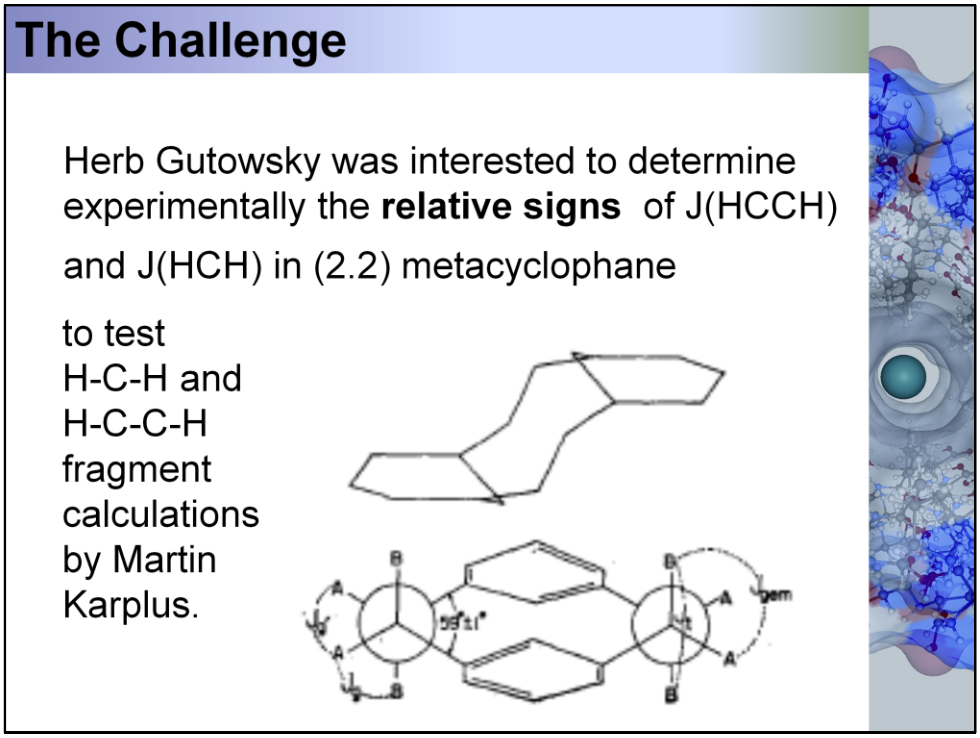
$^2J(HCH)$ decreases from 32 cps to 0 cps for HCH angles of 100° to 125°, becomes negative for angles greater than 125°

J. Chem. Phys. 30, 11 (1959)

J. Chem. Phys. 31, 1278 (1959)

Image from CalTech archives

The only calculations available at the time was by Martin Karplus for the H-C-C-H fragment (M. Karplus, Contact electron–spin coupling of nuclear magnetic moments. J. Chem. Phys., **1959**, 30, 11–15, the famed ‘Karplus equation” This is a citation classic (as last recorded in 1961-1972) M. Karplus, Vicinal proton coupling in nuclear magnetic resonance. J. Am. Chem. Soc. 1963, 85, 2870–2871. $^3J(HCCH) = A\cos 2\phi + B\cos\phi + C$, ϕ= dihedral angle) and the H-C-H fragment led to positive values. Apparently, in 1958, while Martin Karplus was in the process of completing his seminal 1959 paper on the theoretical dependence of vicinal NMR coupling constants on the dihedral angle of the coupled protons, he attended a lecture by the late Raymond Lemieux at the University of Illinois in May, 1958 and recognized that Lemieux’s new experimental data for such couplings in carbohydrates and cyclohexenes fitted his theoretical results very well. It was not long before a number of other sugar chemists started exploiting this angular dependence of coupling constants in the conformational and configurational analysis of carbohydrates and their derivatives, and the Karplus equation has found wide acceptance and utility throughout organic and inorganic chemistry not only for HCCH.

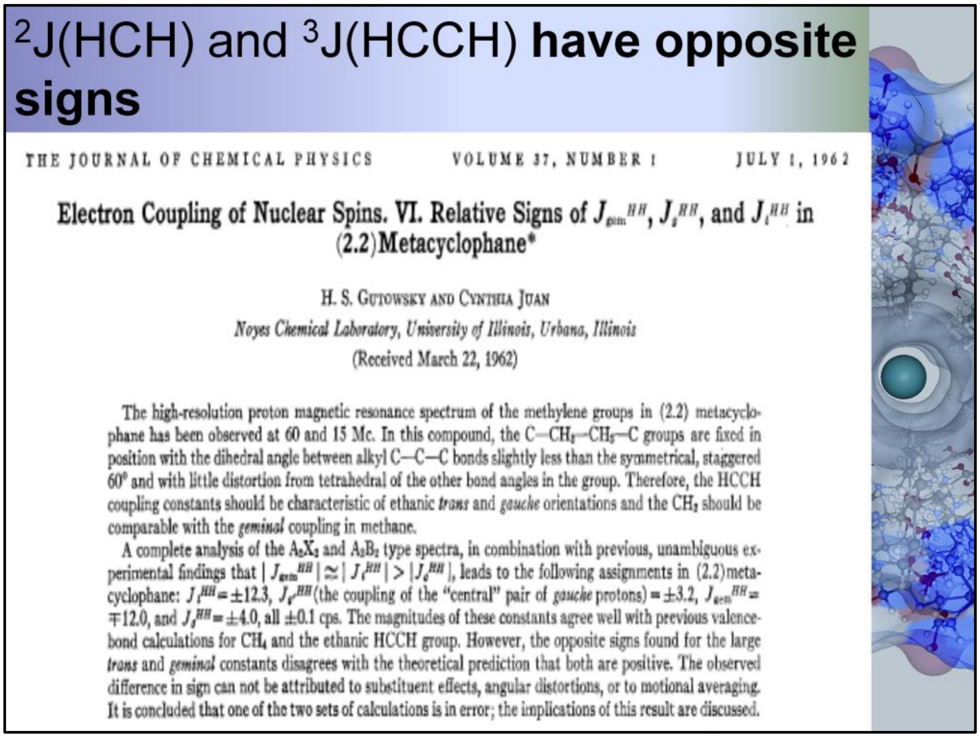


The Challenge

Herb Gutowsky was interested to determine experimentally the **relative signs** of J(HCCH) and J(HCH) in (2.2) metacyclophane

to test H-C-H and H-C-C-H fragment calculations by Martin Karplus.

To test these calculations: No hetero atoms (avoid electronegativity differences, ionic character, effects of lone pairs). No motional averaging: A clear-cut case, dihedral angles rigidly locked in and known, to test H-C-H and H-C-C-H fragment calculations. I obtained the proton spectrum in two fields. We happened to have the only computer code for 6 spins (1/2) nmr spectrum calculations written by Ginevra Belford for the ILIAC I which I used to get an unequivocal match to the experimental spectra.



^2J(HCH) and ^3J(HCCH) **have opposite signs**

THE JOURNAL OF CHEMICAL PHYSICS VOLUME 37, NUMBER 1 JULY 1, 1962

Electron Coupling of Nuclear Spins. VI. Relative Signs of J_{gem}^{HH}, J_s^{HH}, and J_t^{HH} in (2.2)Metacyclophane*

H. S. Gutowsky and Cynthia Juan

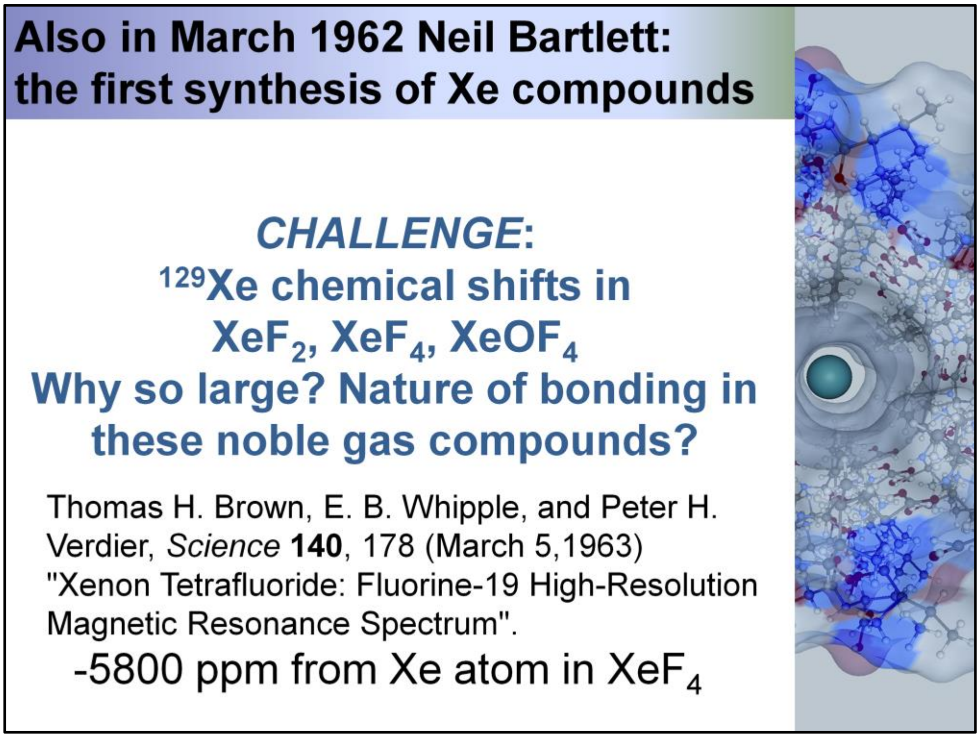
Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

(Received March 22, 1962)

The high-resolution proton magnetic resonance spectrum of the methylene groups in (2.2) metacyclophane has been observed at 60 and 15 Mc. In this compound, the C—CH_2—CH_2—C groups are fixed in position with the dihedral angle between alkyl C—C—C bonds slightly less than the symmetrical, staggered 60° and with little distortion from tetrahedral of the other bond angles in the group. Therefore, the HCCH coupling constants should be characteristic of ethanic *trans* and *gauche* orientations and the CH_2 should be comparable with the *geminal* coupling in methane.

A complete analysis of the A_2X_2 and A_2B_2 type spectra, in combination with previous, unambiguous experimental findings that $|J_{gem}^{HH}| \simeq |J_t^{HH}| > |J_g^{HH}|$, leads to the following assignments in (2.2)metacyclophane: $J_t^{HH} = \pm 12.3$, $J_{g'}^{HH}$(the coupling of the "central" pair of *gauche* protons) $= \pm 3.2$, $J_{gem}^{HH} = \mp 12.0$, and $J_s^{HH} = \pm 4.0$, all ± 0.1 cps. The magnitudes of these constants agree well with previous valence-bond calculations for CH_4 and the ethanic HCCH group. However, the opposite signs found for the large *trans* and *geminal* constants disagrees with the theoretical prediction that both are positive. The observed difference in sign can not be attributed to substituent effects, angular distortions, or to motional averaging. It is concluded that one of the two sets of calculations is in error; the implications of this result are discussed.

Herb sat on my manuscript for a long time because he did not believe my results were unequivocal, until he and Dave Grant did a paper on a comprehensive analysis of AA’BB’ to A2X2 systems themselves.



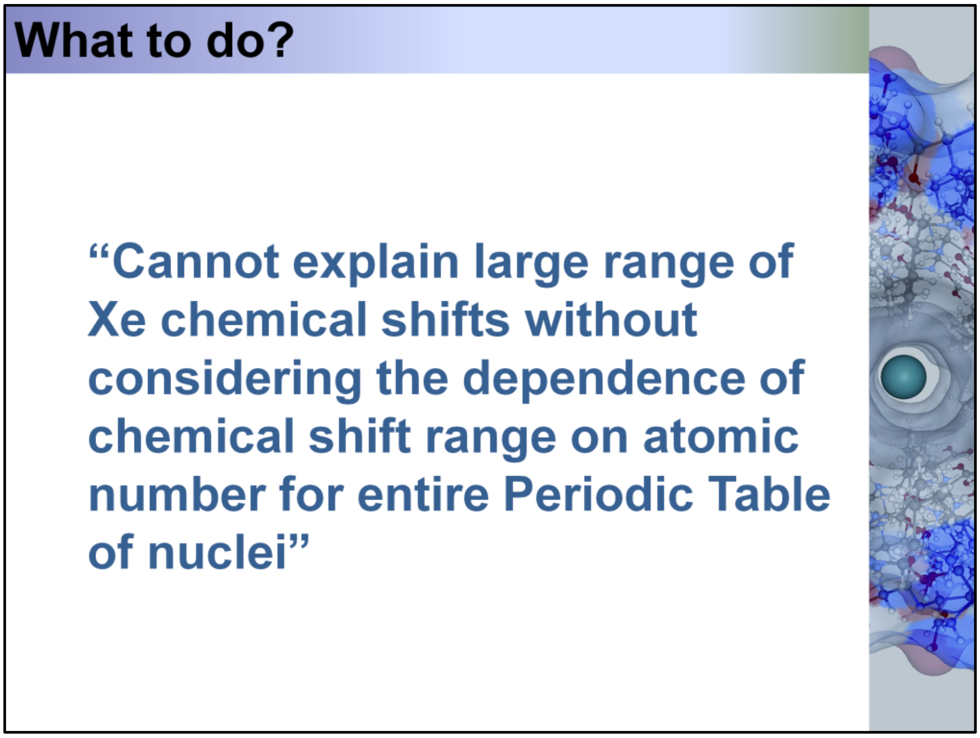
Also in March 1962 Neil Bartlett: the first synthesis of Xe compounds

CHALLENGE:
^{129}Xe chemical shifts in
XeF_2, XeF_4, $XeOF_4$
Why so large? Nature of bonding in these noble gas compounds?

Thomas H. Brown, E. B. Whipple, and Peter H. Verdier, *Science* **140**, 178 (March 5,1963) "Xenon Tetrafluoride: Fluorine-19 High-Resolution Magnetic Resonance Spectrum".

-5800 ppm from Xe atom in XeF_4

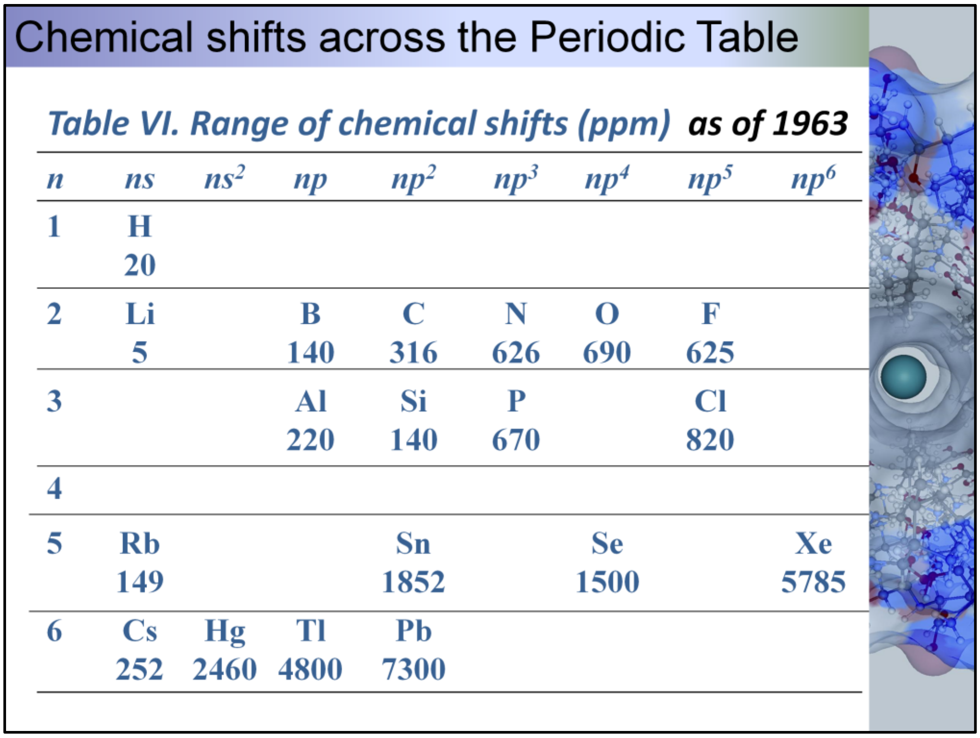
Is this a different type of chemical bond unlike other covalent bonds? NMR to the rescue at Union Carbide Research Institute (those were the days) Varian high-resolution ensemble, with fixed frequencies of 56.44 and 15.00 Mcy/sec and 10-mm non-spinning probe inserts. F-19 spectrum symmetrically split by F coupling to 129 Xe about a stronger center line (all other Xe isotopes) which is shifted 175.0+-1.5 ppm downfield from the solvent (anhydrous HF); the field-independent splitting between the outer lines is 3860+-20 cy/sec. Perturbations of the doublet lines when a second radiofrequency is introduced in the vicinity of the Xe-129 resonance frequency. From such experiments we can infer the presence of four fluorine atoms in the molecule and calculate a Xe-129 chemical shift of about -5800 ppm from atomic xenon. This Herb Gutowsky learned from Tom Brown before it was known to others. Tom had worked with Herb on T depenedence of spin relaxation in aq. solns of paramagnetic ions.



What to do?

“Cannot explain large range of Xe chemical shifts without considering the dependence of chemical shift range on atomic number for entire Periodic Table of nuclei”

Gutowsky gave me this challenge before the paper came out in Science and this is what I said. Then I got married and left Urbana-Champaign to join my husband in NJ. I already had 4 papers on coupling constants, but I needed to write a thesis. Gutowsky made it clear that I need to write it on something other than the 4 papers already published.

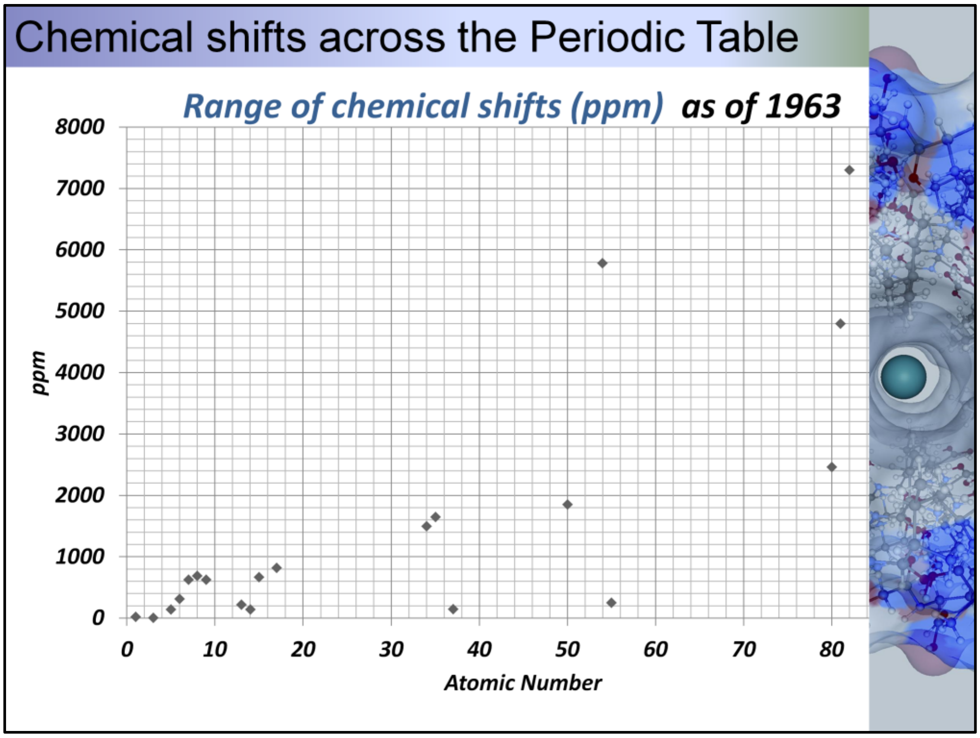


Chemical shifts across the Periodic Table

Table VI. Range of chemical shifts (ppm) ***as of 1963***

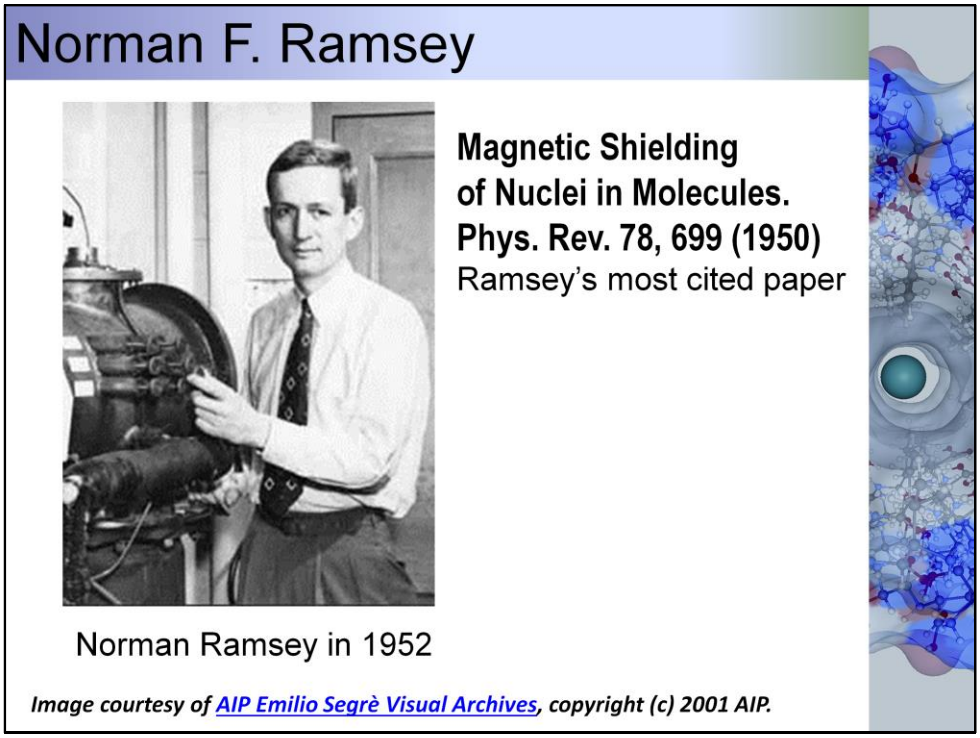
n	*ns*	ns^2	*np*	np^2	np^3	np^4	np^5	np^6
1	H 20							
2	Li 5		B 140	C 316	N 626	O 690	F 625	
3			Al 220	Si 140	P 670		Cl 820	
4								
5	Rb 149			Sn 1852		Se 1500		Xe 5785
6	Cs 252	Hg 2460	Tl 4800	Pb 7300				

Only these 19 nuclei had been observed plus transition metal nuclei Pt, Co



Chemical shifts across the Periodic Table

The observed chemical shift ranges of these nuclei plotted against atomic number looked like there might be a trend across the row, and an amplification of this trend with increasing row number. But, the data was pretty sparse at high Z.



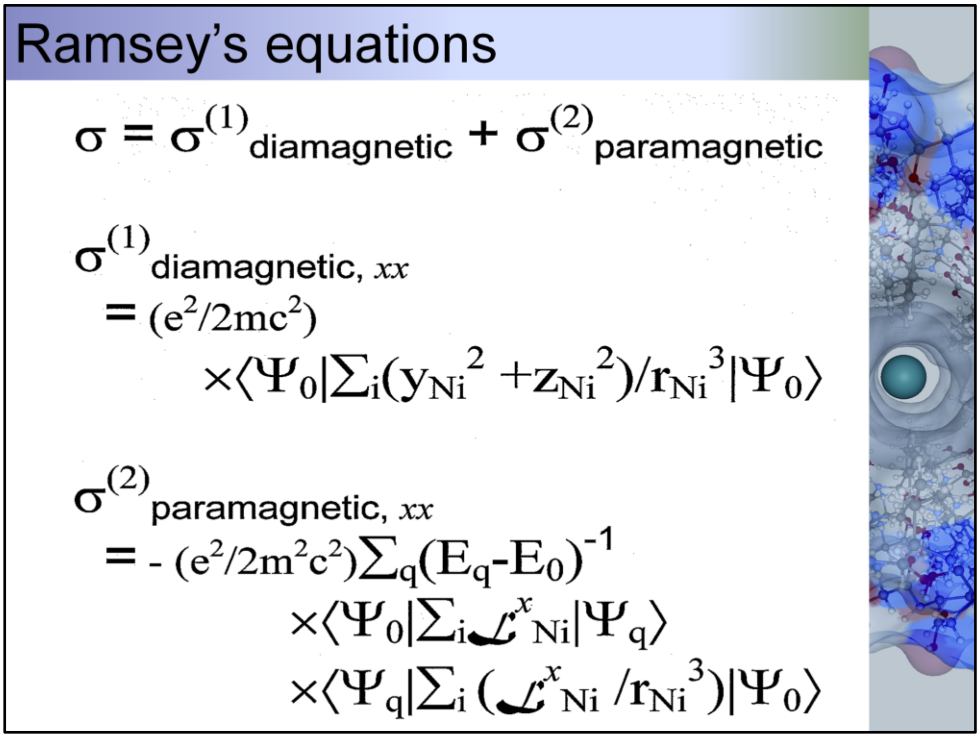
Norman F. Ramsey

Magnetic Shielding of Nuclei in Molecules. Phys. Rev. 78, 699 (1950)
Ramsey's most cited paper

Norman Ramsey in 1952

Image courtesy of AIP Emilio Segrè Visual Archives, copyright (c) 2001 AIP.

Norman F. Ramsey Nobel Prize in 1989 for his work on the hydrogen maser and the atomic clock. But for NMR he developed the first successful theory of chemical shifts and spin spin coupling Ramsey's most cited paper: Magnetic Shielding of Nuclei in Molecules. Phys. Rev. 78, 699 (1950). Later followed by Chemical Effects in Nuclear Magnetic Resonance and in Diamagnetic Susceptibility. Phys. Rev. 86, 243 (1952). "The primary reason that the paper has become one of the most cited is that it provides the fundamental theoretical basis for all later work on nuclear magnetic shielding and on the chemical shifts of NMR that have made NMR such a powerful tool for analysis in chemistry, physics, and biology ."



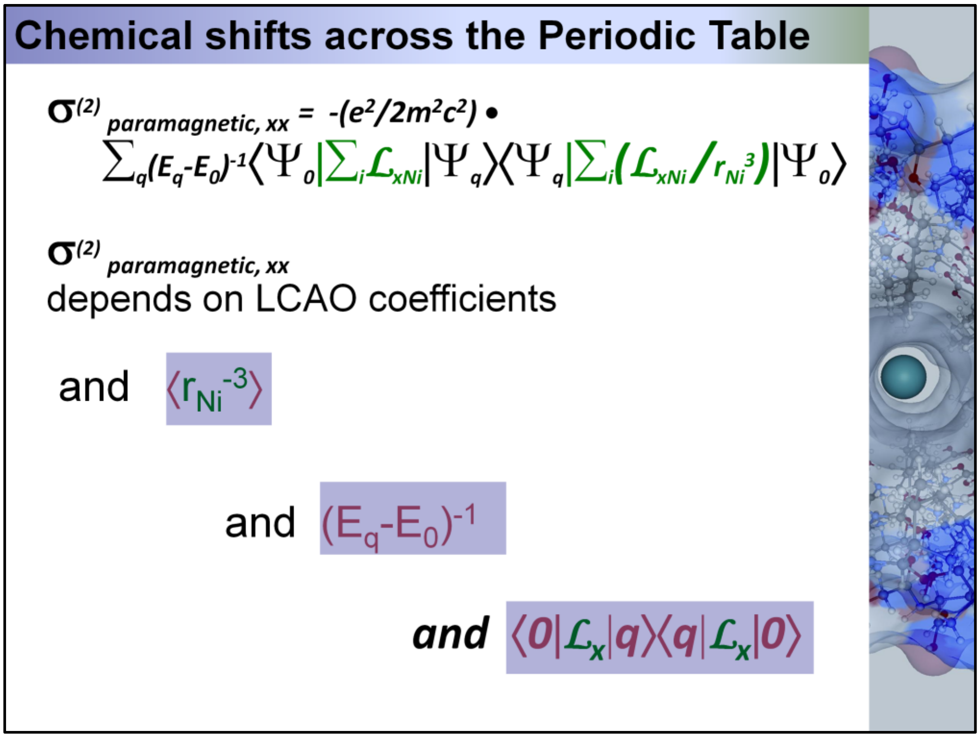
Ramsey's equations

$$\sigma = \sigma^{(1)}{}_{\text{diamagnetic}} + \sigma^{(2)}{}_{\text{paramagnetic}}$$

$$\sigma^{(1)}{}_{\text{diamagnetic},\,xx} = (e^2/2mc^2) \times \langle \Psi_0 | \Sigma_i (y_{Ni}{}^2 + z_{Ni}{}^2)/\mathbf{r}_{Ni}{}^3 | \Psi_0 \rangle$$

$$\sigma^{(2)}{}_{\text{paramagnetic},\,xx} = -\,(e^2/2m^2c^2)\Sigma_q(E_q - E_0)^{-1} \times \langle \Psi_0 | \Sigma_i \mathcal{L}^x{}_{Ni} | \Psi_q \rangle \times \langle \Psi_q | \Sigma_i\, (\mathcal{L}^x{}_{Ni} / \mathbf{r}_{Ni}{}^3) | \Psi_0 \rangle$$

I figured I could not explain why the Xe chemical shifts were so large unless I can also with the same formulation explain the magnitudes of the chemical shifts for the rest of the Periodic Table
So I stared at the Ramsey equations and tried to figure out how to meet Gutowsky's challenge. Centered on the nucleus in question, the diamagnetic part in molecules needed only a small correction to the atomic shielding, because the greatest contributions to the diamagnetic part come from the core. This meant to me that from one molecule to another, only a small part of the differences in nuclear magnetic shielding can come from the diamagnetic part. Larger changes are expected in the paramagnetic part; therefore this is what I stared at.



Chemical shifts across the Periodic Table

$$\sigma^{(2)}_{paramagnetic,\,xx} = -(e^2/2m^2c^2) \bullet \sum_q (E_q - E_0)^{-1} \langle \Psi_0 | \sum_i \mathcal{L}_{xNi} | \Psi_q \rangle \langle \Psi_q | \sum_i (\mathcal{L}_{xNi}/r_{Ni}^3) | \Psi_0 \rangle$$

$\sigma^{(2)}_{paramagnetic,\,xx}$
depends on LCAO coefficients

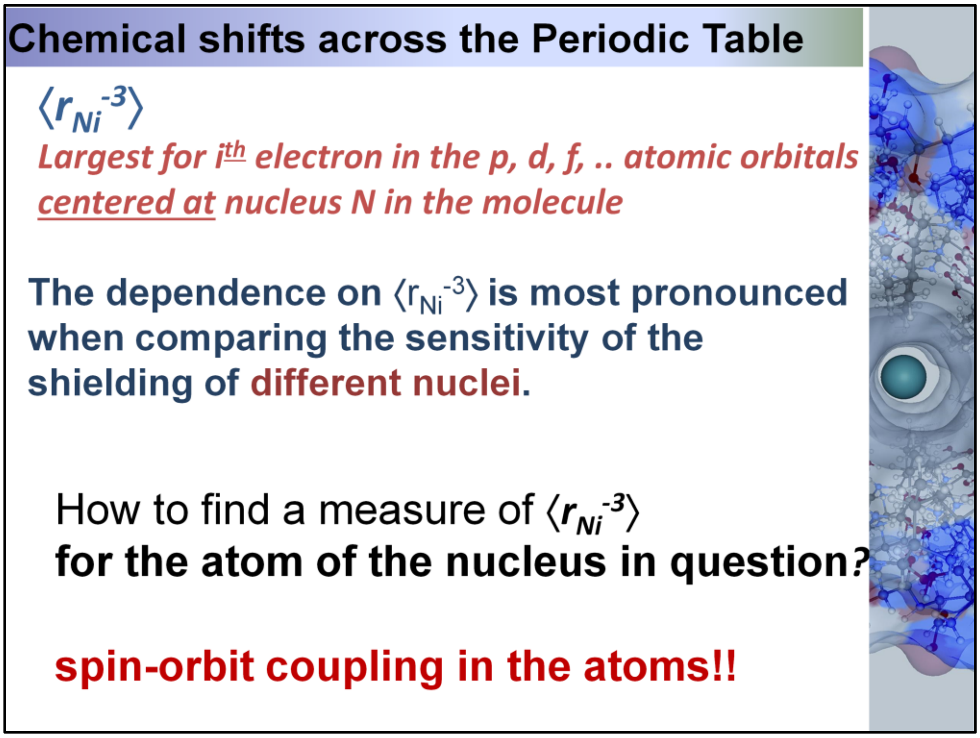
and $\langle r_{Ni}^{-3} \rangle$

and $(E_q - E_0)^{-1}$

and $\langle 0 | \mathcal{L}_x | q \rangle \langle q | \mathcal{L}_x | 0 \rangle$

The angular momentum operators work only on the angular parts of the wavefunctions, and I evaluated all the possible integrals between p and d atomic orbitals that would be needed. But there was a r_{Ni}^{-3} operator that worked on the radial parts of the wavefunctions and actually, the excited states would have to be summed over. Naively I thought that a very simplified result could arise if there is a dominant low-lying excited state or if the low-lying excited states that dominate the contributions have nearly the same energy so I could use an average energy approximation. At this time Karplus had already suggested the use of the ‘mean energy approximation’ for J calculations *J. Chem. Phys.* 33, 941-942 (**1960**). Another naïve idea was that once I invoke the average energy approximation the integration over the radial parts that I would need would involve only those functions which provide non-vanishing angular momentum integrals, that is, the p and d orbitals, and I could carry out a complete calculation using the coefficients of the atomic orbitals in the MOs. It is these coefficients that that from one molecule to another, but all integrations over the radial and angular parts will be over the constituent atomic orbitals. Once I made the average energy approximation leap, everything becomes in terms of atomic integrals $\langle r_{Ni}^{-3} \rangle$ and atomic angular momentum integrals $\langle 0|\mathbf{L}_x|q\rangle\langle q|\mathbf{L}_x|0\rangle$ and the LCAO coefficients. Karplus (at this time already at Columbia University) and TP Das had already evaluated these integrals over the p orbitals and published a formulation using LCAO coefficients to consider

F-19 chemical shifts in fluorobenzenes using ideas of ionic character, hybridization and bond order to interpret the observed shifts. J. Chem. Phys. 34, 1683 (**1961**). I needed to extend my formulation to d orbitals to include the observed nuclei.



Chemical shifts across the Periodic Table

$\langle r_{Ni}^{-3} \rangle$

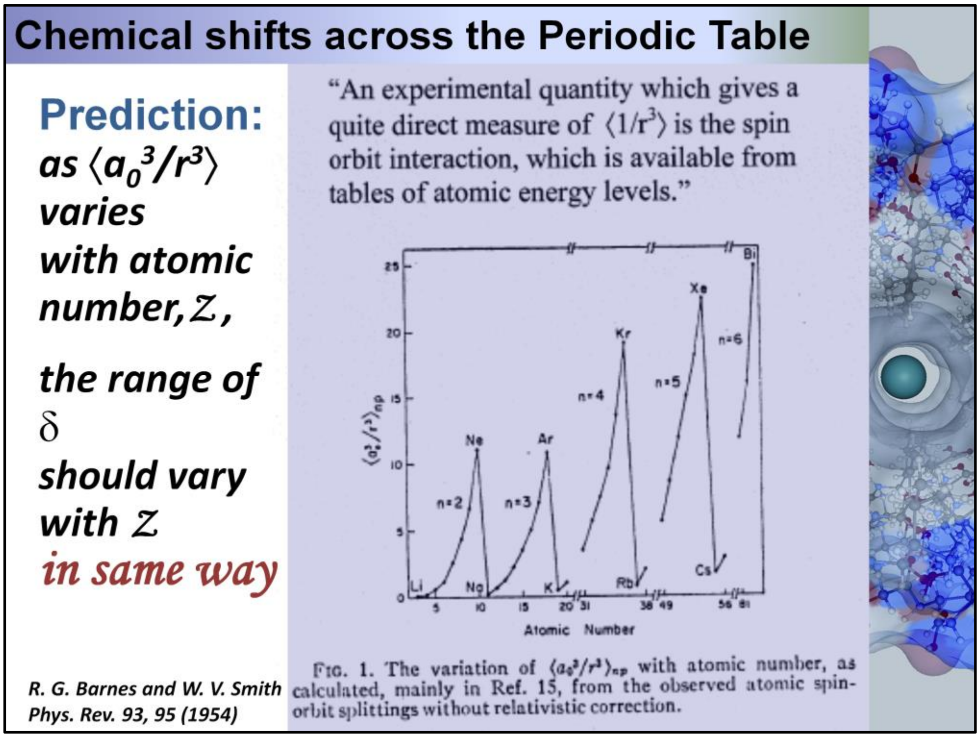
Largest for ith electron in the p, d, f, .. atomic orbitals centered at nucleus N in the molecule

The dependence on $\langle r_{Ni}^{-3} \rangle$ is most pronounced when comparing the sensitivity of the shielding of different nuclei.

How to find a measure of $\langle r_{Ni}^{-3} \rangle$
for the atom of the nucleus in question?

spin-orbit coupling in the atoms!!

I just needed to find an atomic observable that would provide me with these $\langle r_{Ni}^{-3} \rangle$ values for all atoms in the Periodic Table.



Chemical shifts across the Periodic Table

Prediction:
as $\langle a_0^3/r^3\rangle$ varies with atomic number, $\mathcal{Z}$,

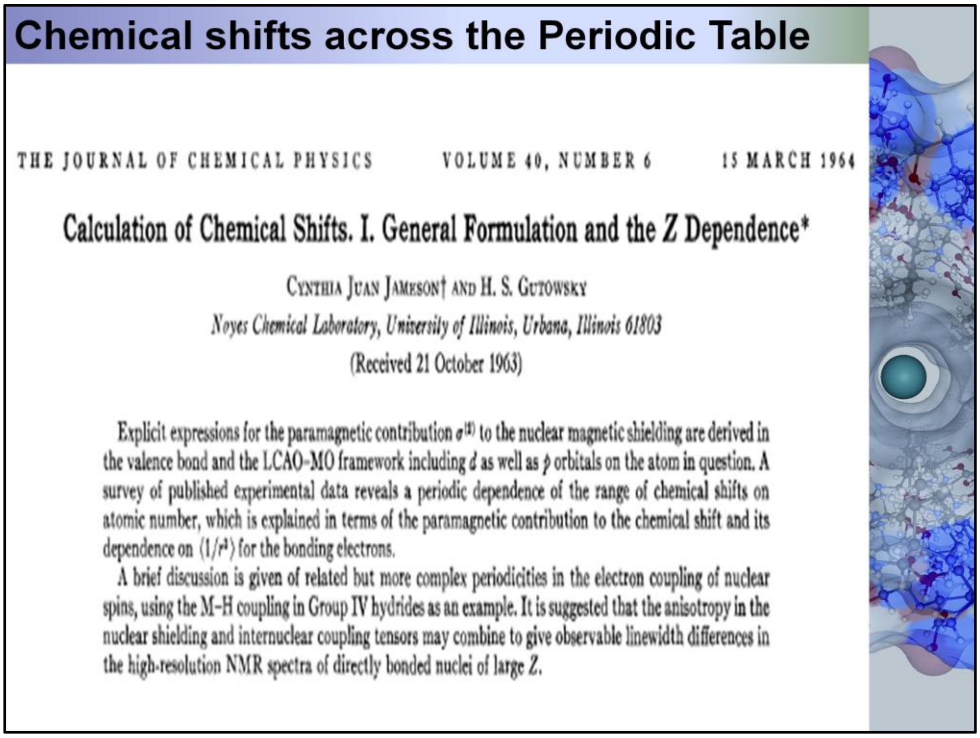
the range of δ should vary with $\mathcal{Z}$
in same way

"An experimental quantity which gives a quite direct measure of $\langle 1/r^3\rangle$ is the spin orbit interaction, which is available from tables of atomic energy levels."

FIG. 1. The variation of $\langle a_0^3/r^3\rangle_{np}$ with atomic number, as calculated, mainly in Ref. 15, from the observed atomic spin-orbit splittings without relativistic correction.

R. G. Barnes and W. V. Smith
Phys. Rev. 93, 95 (1954)

The values are from Barnes and Smith 1954 taken from observed spin-orbit splittings in the atomic spectrum using Russell-Saunders L-S coupling, and I calculated others using j-j coupling where that applies. I discovered the Barnes and Smith paper accidentally while browsing Phys. Rev. in the library at Columbia University.



Chemical shifts across the Periodic Table

THE JOURNAL OF CHEMICAL PHYSICS VOLUME 40, NUMBER 6 15 MARCH 1964

Calculation of Chemical Shifts. I. General Formulation and the Z Dependence*

CYNTHIA JUAN JAMESON† AND H. S. GUTOWSKY

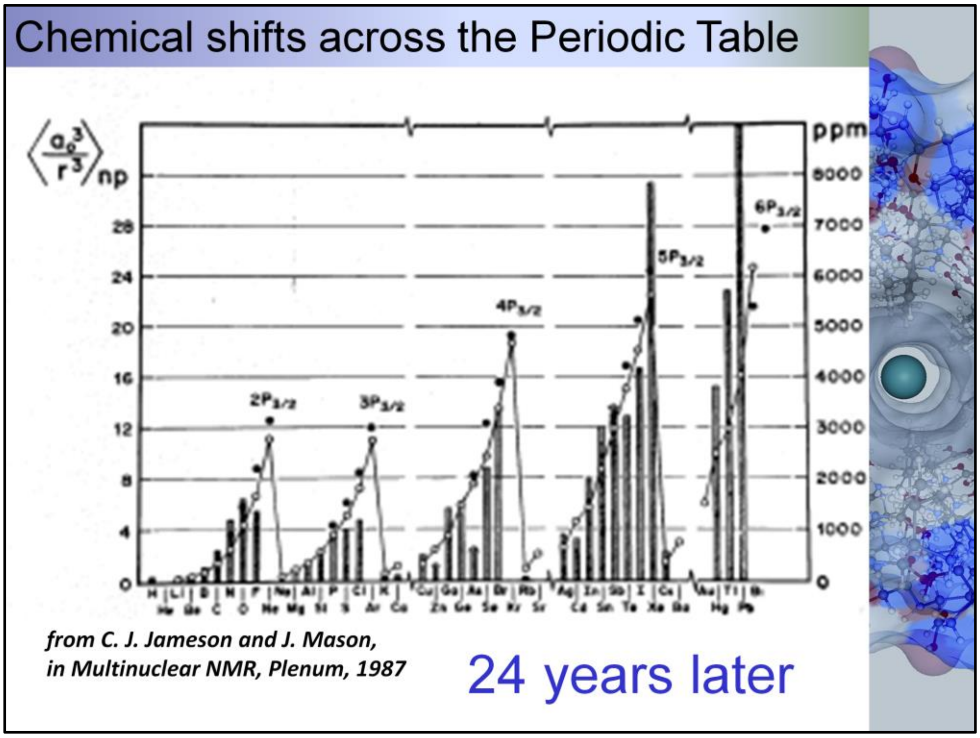
Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois 61803

(Received 21 October 1963)

Explicit expressions for the paramagnetic contribution $\sigma^{(2)}$ to the nuclear magnetic shielding are derived in the valence bond and the LCAO-MO framework including d as well as p orbitals on the atom in question. A survey of published experimental data reveals a periodic dependence of the range of chemical shifts on atomic number, which is explained in terms of the paramagnetic contribution to the chemical shift and its dependence on $\langle 1/r^3 \rangle$ for the bonding electrons.

A brief discussion is given of related but more complex periodicities in the electron coupling of nuclear spins, using the M–H coupling in Group IV hydrides as an example. It is suggested that the anisotropy in the nuclear shielding and internuclear coupling tensors may combine to give observable linewidth differences in the high-resolution NMR spectra of directly bonded nuclei of large Z.

So I did the calculations of the angular momentum integrals and wrote out the equations and my dissertation and my husband typed it and I sent it to Herb "Theoretical Calculations of Chemical Shifts in NMR. Application to the Xenon Fluorides" . I also wrote out the 2 papers for JCP this is the first one and the second was "II. The xenon fluorides." His first question was: Is Keith still speaking to you?

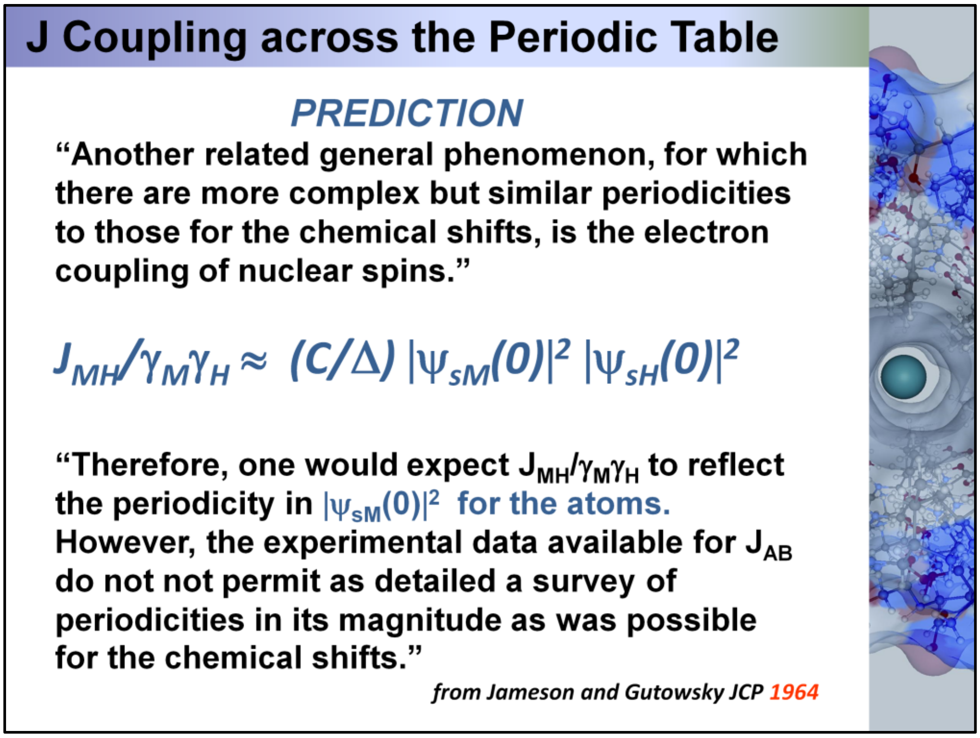


Chemical shifts across the Periodic Table

from C. J. Jameson and J. Mason,
in Multinuclear NMR, Plenum, 1987

24 years later

I am sure there are recent additions to this compilation in 1987, but this was good enough to show that my ideas were sensible and useful.



J Coupling across the Periodic Table

PREDICTION

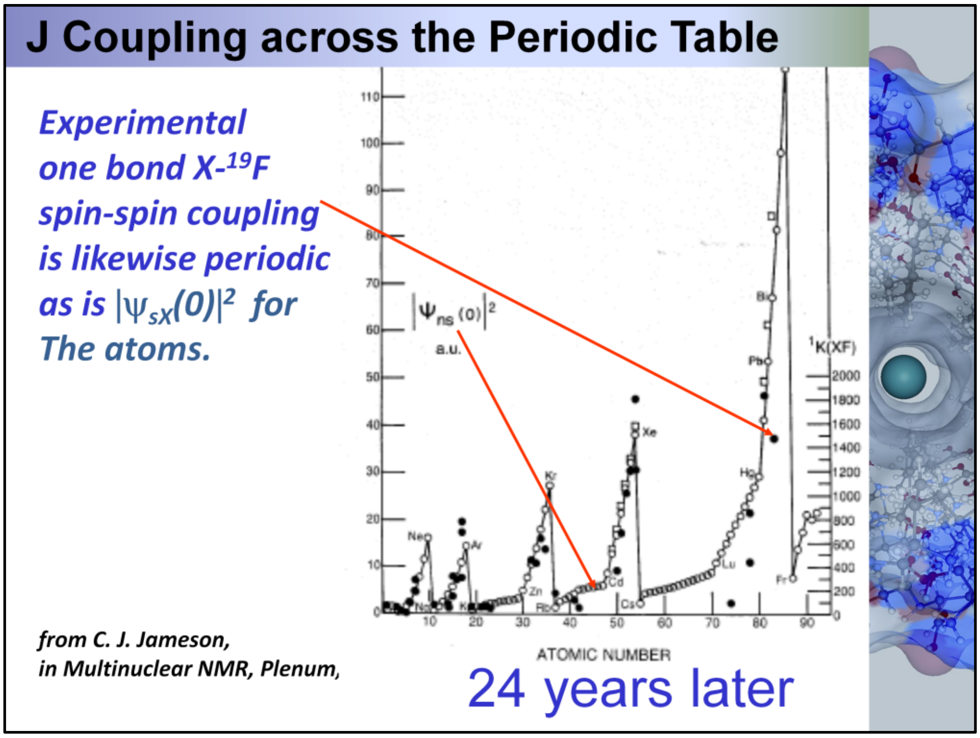
"Another related general phenomenon, for which there are more complex but similar periodicities to those for the chemical shifts, is the electron coupling of nuclear spins."

$$J_{MH}/\gamma_M\gamma_H \approx (C/\Delta)\,|\psi_{sM}(0)|^2\,|\psi_{sH}(0)|^2$$

"Therefore, one would expect $J_{MH}/\gamma_M\gamma_H$ to reflect the periodicity in $|\psi_{sM}(0)|^2$ for the atoms. However, the experimental data available for J_{AB} do not not permit as detailed a survey of periodicities in its magnitude as was possible for the chemical shifts."

from Jameson and Gutowsky JCP 1964

In the same paper, Gutowsky added this prediction.



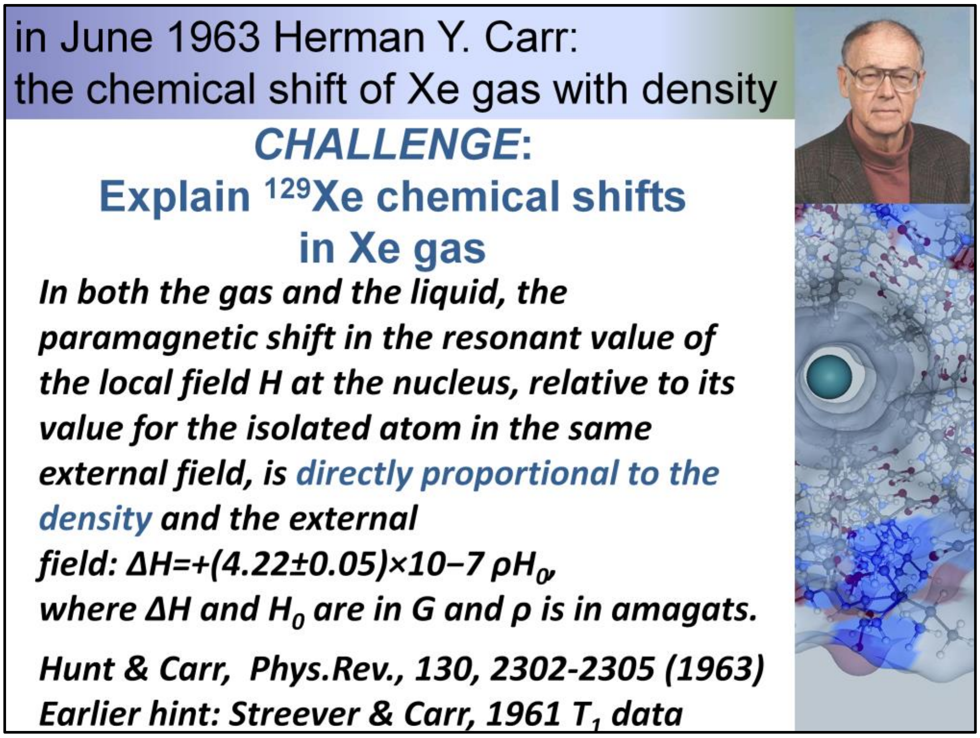
J Coupling across the Periodic Table

Experimental one bond X-^{19}F spin-spin coupling is likewise periodic as is $|\psi_{sX}(0)|^2$ for The atoms.

from C. J. Jameson, in Multinuclear NMR, Plenum,

24 years later

F-19 has the most other atom types to which it bonds so I made these calculations and collected the data in 1987 to make a good test of the predictions we made in 1964.



in June 1963 Herman Y. Carr: the chemical shift of Xe gas with density

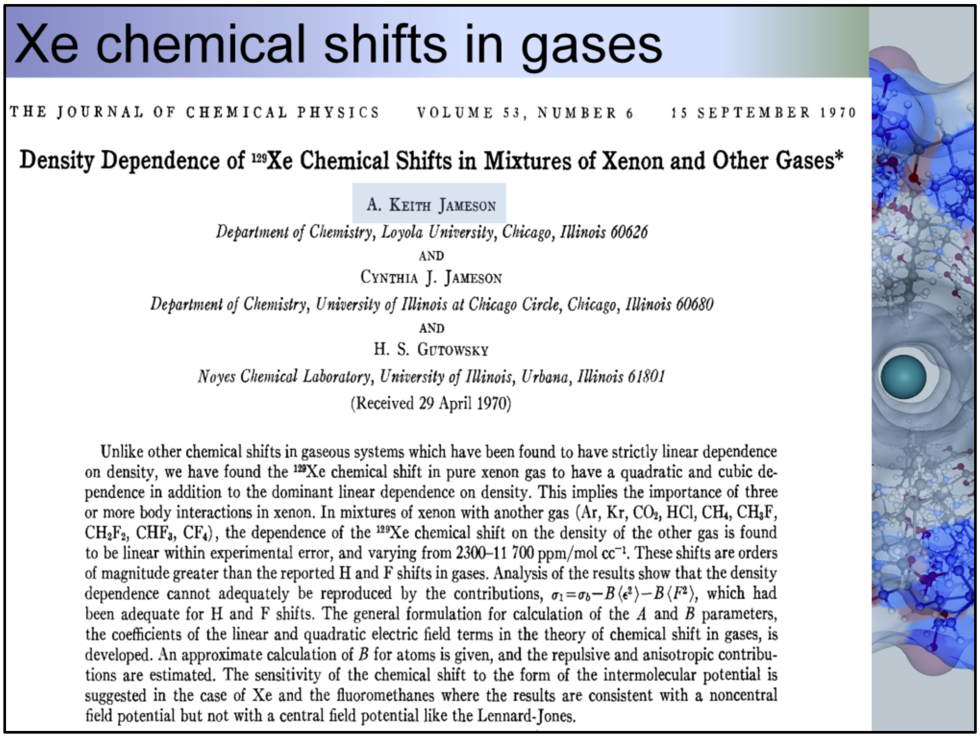
***CHALLENGE*:**

Explain ^{129}Xe chemical shifts in Xe gas

In both the gas and the liquid, the paramagnetic shift in the resonant value of the local field H at the nucleus, relative to its value for the isolated atom in the same external field, is directly proportional to the density and the external field: $\Delta H=+(4.22\pm0.05)\times10-7\ \rho H_0$, where ΔH and H_0 are in G and ρ is in amagats.

Hunt & Carr, Phys.Rev., 130, 2302-2305 (1963)
Earlier hint: Streever & Carr, 1961 T_1 data

I ran into the Hunt and Carr paper of 1963 **accidentally** while browsing in the library at Columbia U. and I thought, that is a large Xe intermolecular shift with density. To the graduate students in the audience: Notice how serendipity plays a role in the doing of science; especially for a prepared mind. I told my brand new husband Keith Jameson (at that time working for Esso in NJ) about it. This work by Carr started Keith and myself on our career-long journey using Xe atom as a probe.
Later, E. Kanegsberg, B. Pass, and H. Y. Carr, Phys. Rev. Lett. **23**, 572 September 1969 measured the temperature dependence of the shift per unit density in the low-density limit.



Xe chemical shifts in gases

THE JOURNAL OF CHEMICAL PHYSICS VOLUME 53, NUMBER 6 15 SEPTEMBER 1970

Density Dependence of ^{129}Xe Chemical Shifts in Mixtures of Xenon and Other Gases*

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AND
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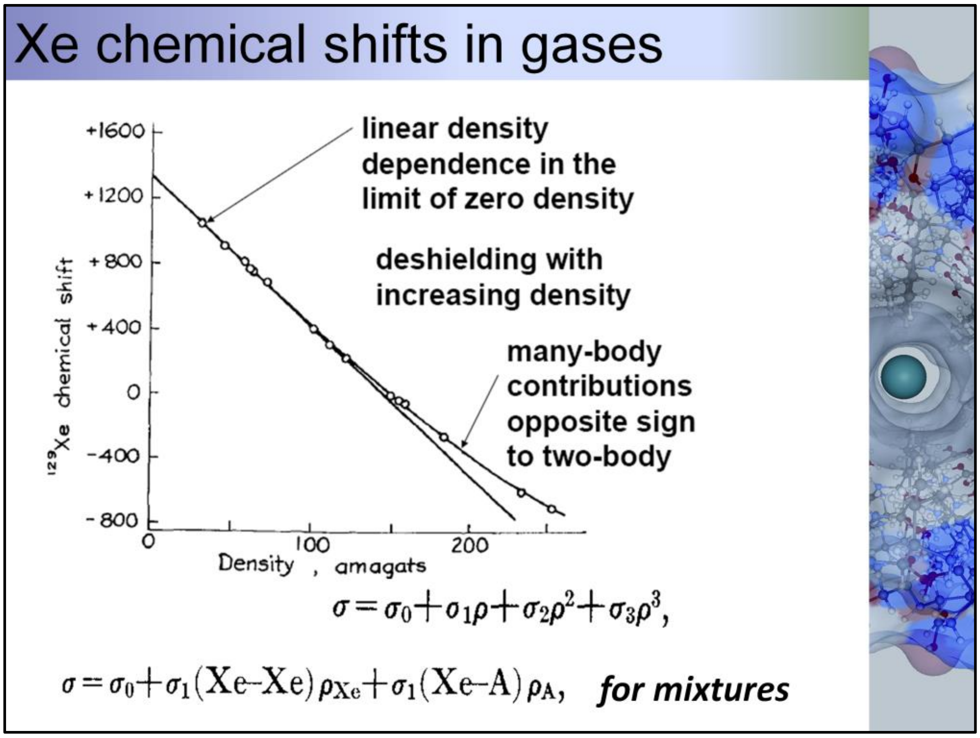
Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois 61801

(Received 29 April 1970)

Unlike other chemical shifts in gaseous systems which have been found to have strictly linear dependence on density, we have found the ^{129}Xe chemical shift in pure xenon gas to have a quadratic and cubic dependence in addition to the dominant linear dependence on density. This implies the importance of three or more body interactions in xenon. In mixtures of xenon with another gas (Ar, Kr, CO_2, HCl, CH_4, CH_3F, CH_2F_2, CHF_3, CF_4), the dependence of the ^{129}Xe chemical shift on the density of the other gas is found to be linear within experimental error, and varying from 2300–11 700 ppm/mol cc^{-1}. These shifts are orders of magnitude greater than the reported H and F shifts in gases. Analysis of the results show that the density dependence cannot adequately be reproduced by the contributions, $\sigma_1 = \sigma_b - B\langle\epsilon^2\rangle - B\langle F^2\rangle$, which had been adequate for H and F shifts. The general formulation for calculation of the A and B parameters, the coefficients of the linear and quadratic electric field terms in the theory of chemical shift in gases, is developed. An approximate calculation of B for atoms is given, and the repulsive and anisotropic contributions are estimated. The sensitivity of the chemical shift to the form of the intermolecular potential is suggested in the case of Xe and the fluoromethanes where the results are consistent with a noncentral field potential but not with a central field potential like the Lennard-Jones.

So when my husband and I came back to the US to look for academic jobs after a 2 year stay in the Philippines to satisfy the conditions of my Fulbright exchange visa as a graduate student, we decided this was an interesting subject to work on.



Xe chemical shifts in gases

linear density dependence in the limit of zero density

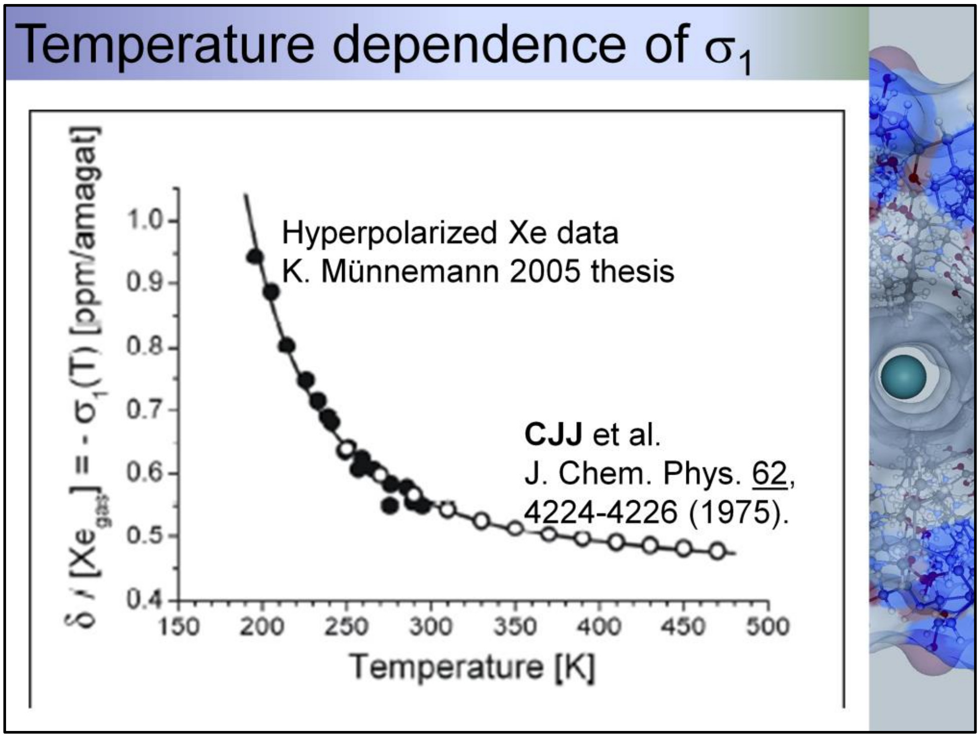
deshielding with increasing density

many-body contributions opposite sign to two-body

$$\sigma = \sigma_0 + \sigma_1\rho + \sigma_2\rho^2 + \sigma_3\rho^3,$$

$$\sigma = \sigma_0 + \sigma_1(\mathrm{Xe{-}Xe})\,\rho_{\mathrm{Xe}} + \sigma_1(\mathrm{Xe{-}A})\,\rho_{\mathrm{A}},$$ ***for mixtures***

Buckingham and Pople had already established that for non-ideal gases, molecular electronic properties could be written in terms of an expansion $\sigma = \sigma_0(T) + \sigma_1(T)\rho + \sigma_2(T)\rho^2 + \sigma_3(T)\rho^3 + \ldots$
Where, for a spherical system such as Xe
$\sigma_1(T) = 4\pi^2 \int \{\sigma(R) - \sigma(\infty)\} \exp [V(R)/kT]$

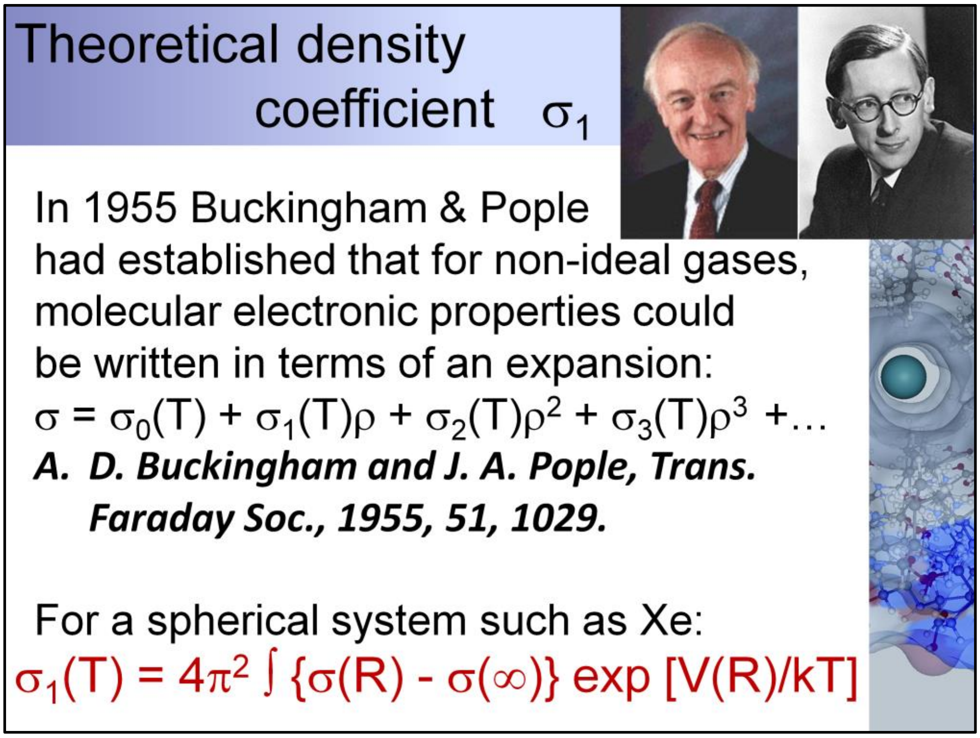


Temperature dependence of σ_1

Hyperpolarized Xe data
K. Münnemann 2005 thesis

CJJ et al.
J. Chem. Phys. 62,
4224-4226 (1975).

Our data in 1975 merges well with 2005 data using hyperpolarized Xe.



Theoretical density coefficient σ_1

In 1955 Buckingham & Pople had established that for non-ideal gases, molecular electronic properties could be written in terms of an expansion:

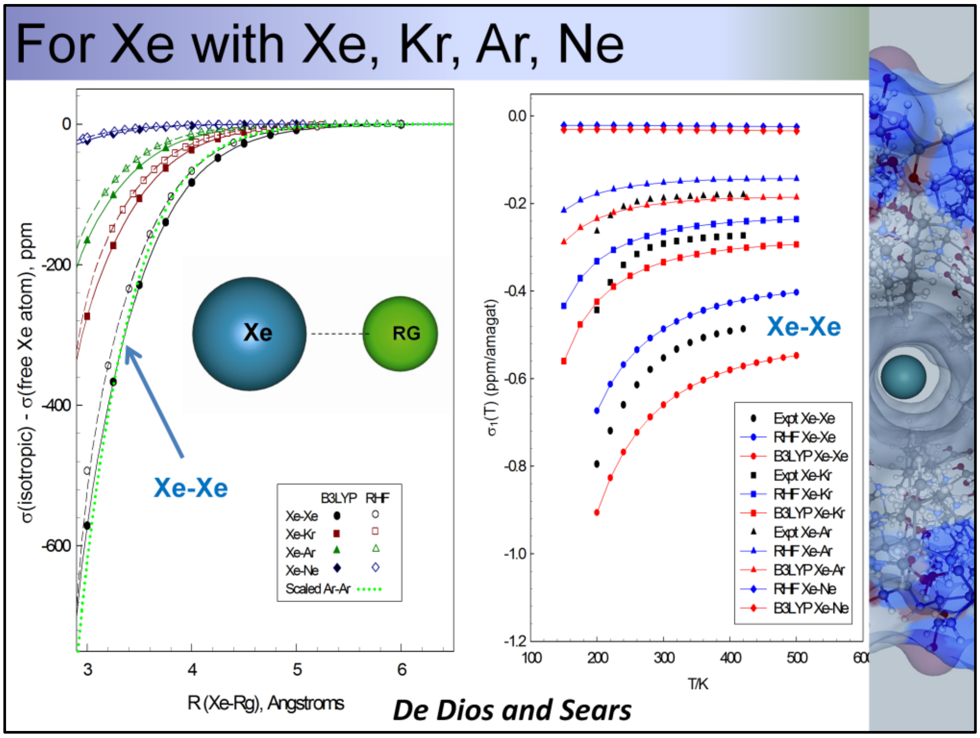
$\sigma = \sigma_0(T) + \sigma_1(T)\rho + \sigma_2(T)\rho^2 + \sigma_3(T)\rho^3 + \ldots$

A. D. Buckingham and J. A. Pople, Trans. Faraday Soc., 1955, 51, 1029.

For a spherical system such as Xe:

$\sigma_1(T) = 4\pi^2 \int \{\sigma(R) - \sigma(\infty)\} \exp [V(R)/kT]$

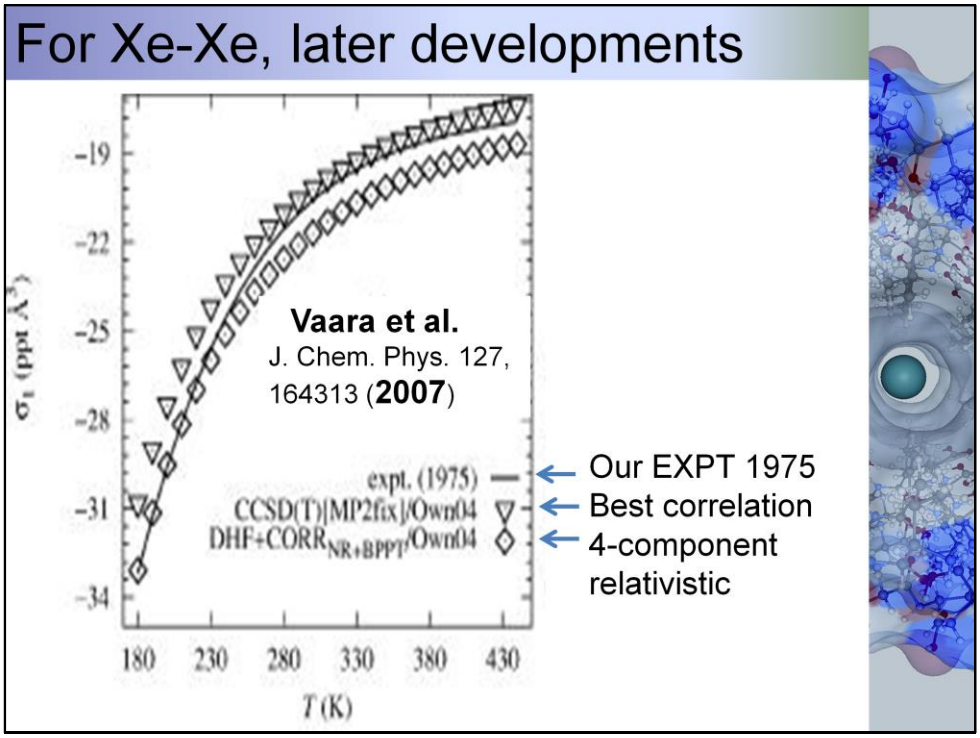
We see from ADB and Pople that we need to calculate the shielding surface $\sigma(R)$ and supply $V(R)$ to be able to reproduce the experimental density coefficient of the chemical shift



For Xe with Xe, Kr, Ar, Ne

De Dios and Sears

By 2003 the best available Xe-Rg potential functions were quite accurate, capable of reproducing even the vibrational spacings of the van der Waals complex. Analysis of the integral finds that the greatest sliver of intermolecular shielding contribution to the density coefficient comes from the region close to 1.08 r_0 **with the bulk of the integral coming from the region (0.92-1.3)r_0 for all rare gas pairs.** What this means is that the potential function has to have the right r_0 and behave correctly in the range 0.92-1.3r_0.in order to be able to interpret accurately the density coefficients.

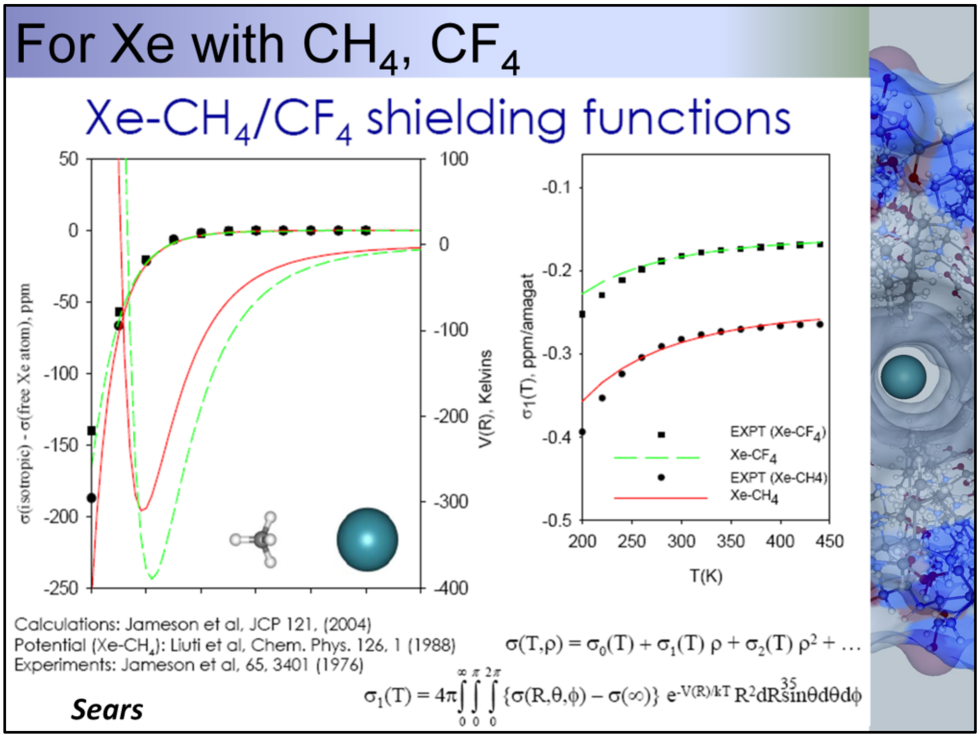


For Xe-Xe, later developments

Vaara et al.
J. Chem. Phys. 127,
164313 (**2007**)

Our EXPT 1975
Best correlation
4-component
relativistic

J. Chem. Phys. 127, 164313 (2007) Vaara et al. Uncorrelated 4-component DHF is corrected with (a) non-relativistic correlation effects at the highest level and then (b) the cross-coupling between electron correlation and relativity is introduced using perturbation theory.



For Xe with CH_4, CF_4

Xe-CH_4/CF_4 shielding functions

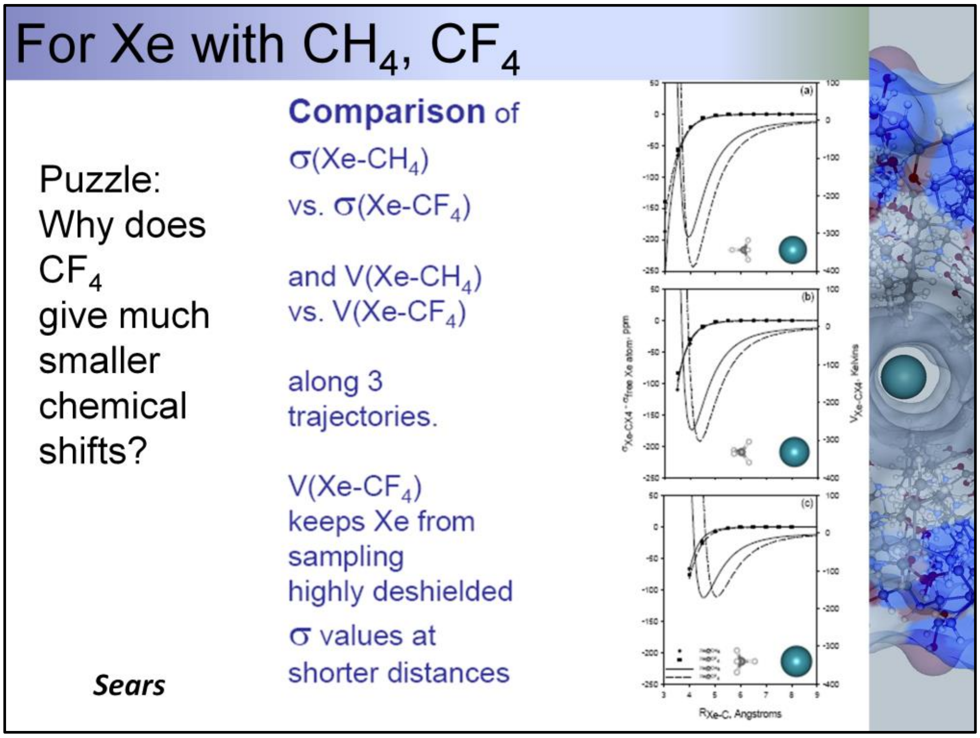
Calculations: Jameson et al, JCP 121, (2004)
Potential (Xe-CH_4): Liuti et al, Chem. Phys. 126, 1 (1988)
Experiments: Jameson et al, 65, 3401 (1976)

$$\sigma(T,\rho) = \sigma_0(T) + \sigma_1(T)\,\rho + \sigma_2(T)\,\rho^2 + \ldots$$

$$\sigma_1(T) = 4\pi \int_0^{\infty}\int_0^{\pi}\int_0^{2\pi} \{\sigma(R,\theta,\phi) - \sigma(\infty)\}\, e^{-V(R)/kT}\, R^2 dR \sin\theta\, d\theta\, d\phi$$

Sears

We also looked at Xe interacting other small molecules.



For Xe with CH_4, CF_4

Puzzle:
Why does
CF_4
give much
smaller
chemical
shifts?

Comparison of
$\sigma(Xe\text{-}CH_4)$
vs. $\sigma(Xe\text{-}CF_4)$

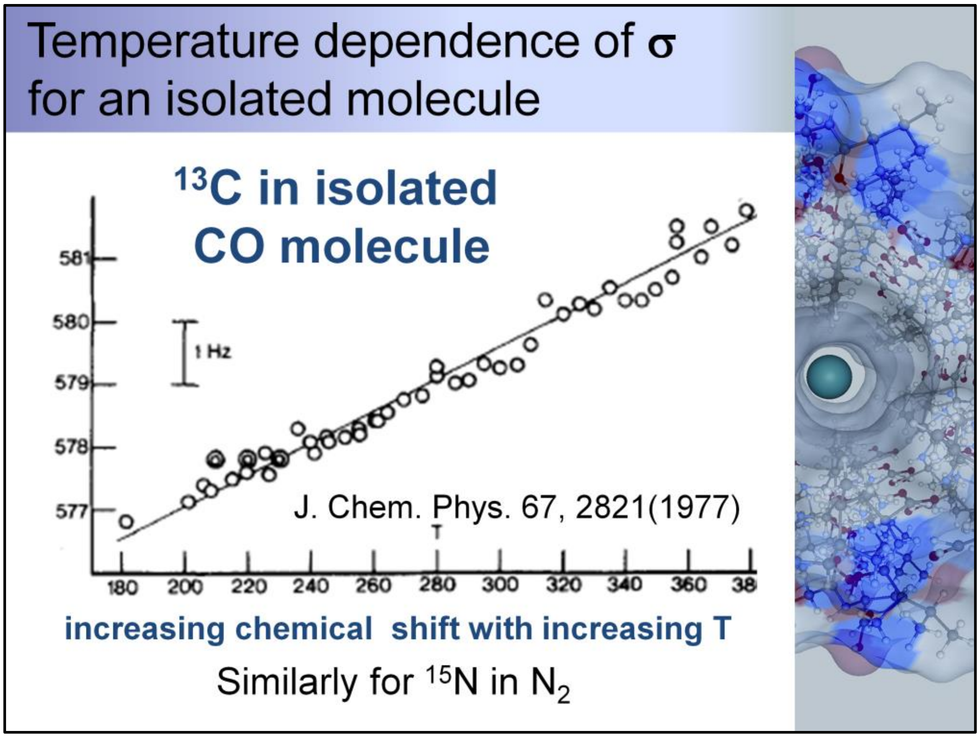
and $V(Xe\text{-}CH_4)$
vs. $V(Xe\text{-}CF_4)$

along 3
trajectories.

$V(Xe\text{-}CF_4)$
keeps Xe from
sampling
highly deshielded
σ values at
shorter distances

Sears

Xe response from CH_4 is about the same and indeed a bit more deshielding only at much shorter distances, but the potential function of Xe-CF_4 keeps Xe from sampling the same regions as Xe-CH_4. It is just as important to know what the probabilities are of finding Xe at close distances, as it is to know how large is the shielding response.



Temperature dependence of σ for an isolated molecule

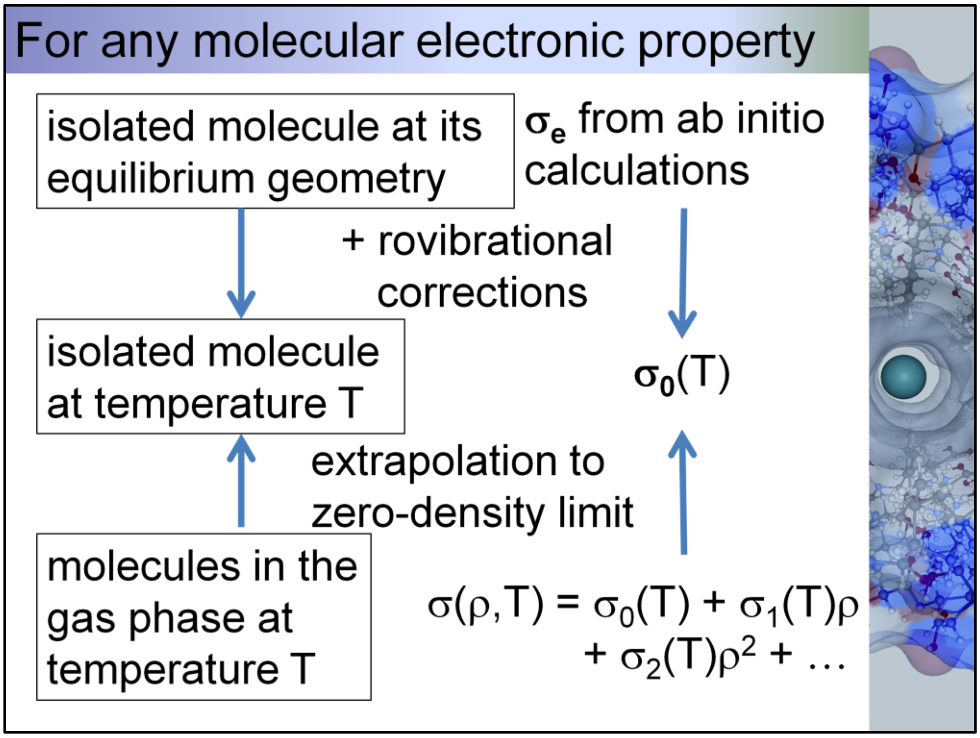
^{13}C in isolated CO molecule

J. Chem. Phys. 67, 2821(1977)

increasing chemical shift with increasing T

Similarly for ^{15}N in N_2

When we started looking at other nuclei than Xe in the gas phase, we discovered that when we extrapolated to zero density as we do in Xe, the chemical shift of the 19F, 13C, 15N, 31P, whatever we looked at in the gas, gave a changing intercept with temperature. After thinking about it a while we decided it must have something to do with the shielding being a function of internal coordinates of a molecule and at various temperatures, the rovibrational average chemical shift is different because the vibrational functions weight different parts of the shielding function.



For any molecular electronic property

isolated molecule at its equilibrium geometry

σ_e from ab initio calculations

+ rovibrational corrections

isolated molecule at temperature T

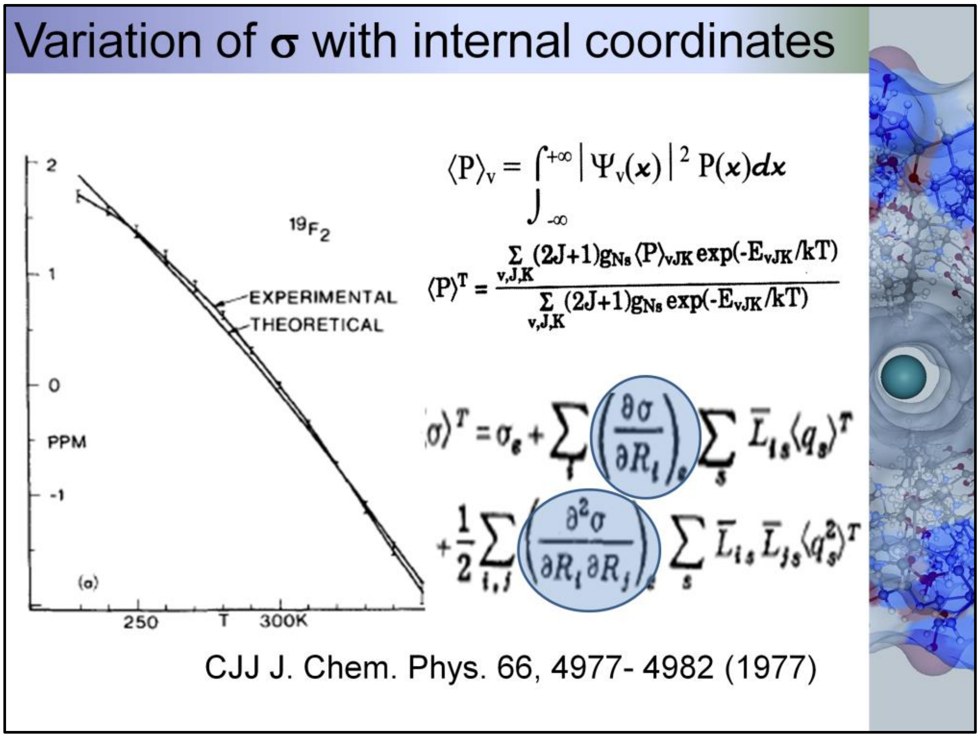
$\sigma_0(T)$

extrapolation to zero-density limit

molecules in the gas phase at temperature T

$$\sigma(\rho,T) = \sigma_0(T) + \sigma_1(T)\rho + \sigma_2(T)\rho^2 + \ldots$$

Of course. Like anything else, David Buckingham had been there before us. He had already thought of a temperature dependent chemical shifts for an isolated molecule in JCP 36, 3096 (1962).



Variation of σ with internal coordinates

$$\langle P\rangle_v = \int_{-\infty}^{+\infty} |\Psi_v(x)|^2 P(x)dx$$

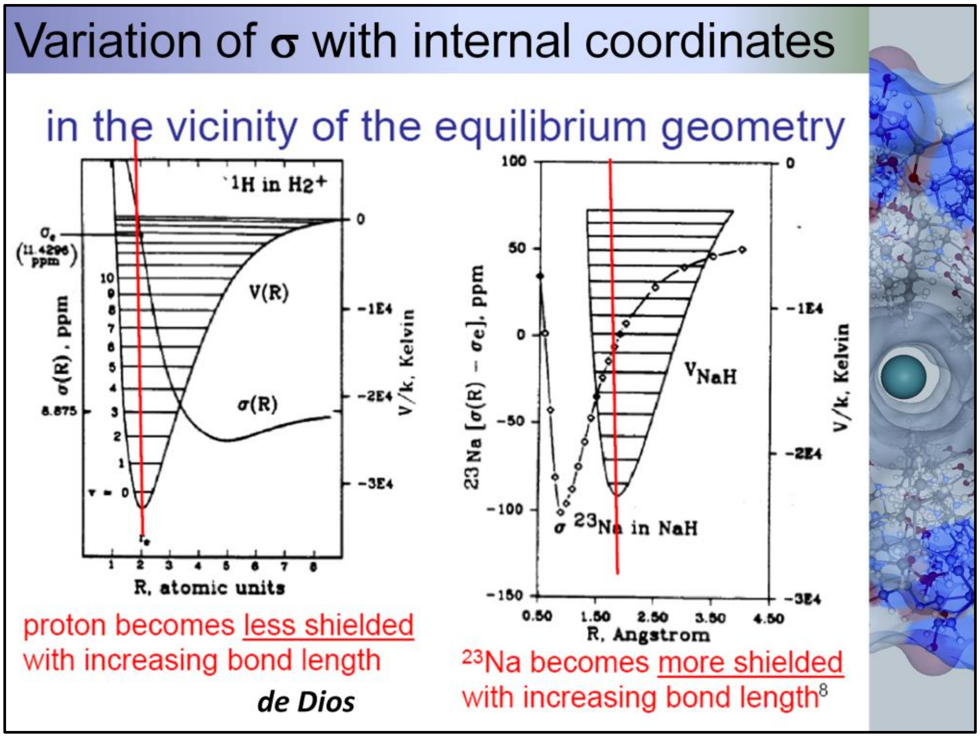
$$\langle P\rangle^T = \frac{\sum_{v,J,K}(2J+1)g_{Ns}\langle P\rangle_{vJK}\exp(-E_{vJK}/kT)}{\sum_{v,J,K}(2J+1)g_{Ns}\exp(-E_{vJK}/kT)}$$

$$\sigma\rangle^T = \sigma_e + \sum_i \left(\frac{\partial\sigma}{\partial R_i}\right)_e \sum_s \bar{L}_{is}\langle q_s\rangle^T$$

$$+\frac{1}{2}\sum_{i,j}\left(\frac{\partial^2\sigma}{\partial R_i \partial R_j}\right)_e \sum_s \bar{L}_{is}\bar{L}_{js}\langle q_s^2\rangle^T$$

CJJ J. Chem. Phys. 66, 4977- 4982 (1977)

We derived the average shielding as a function of temperature, and find the $<q>^T$ and $<q^2>^T$ in terms of quantities that are known from accurate analysis of high-resolution rotational and vibrational spectra of the molecules. **We have products of mass and temperature independent electronic factors and mass and temperature dependent dynamic factors.** Anharmonicity and centrifugal stretching have important roles in $<q>^T$. We measured a large number of temperature dependent chemical shifts in the isolated molecule in the gas phase, including many polyatomic molecules. The quantities that determine whether the chemical shift in the isolated molecule increased or decreased with increasing temperature: $(\partial\sigma/\partial R_i)_e$ is a property of the shielding surface.



Variation of σ with internal coordinates

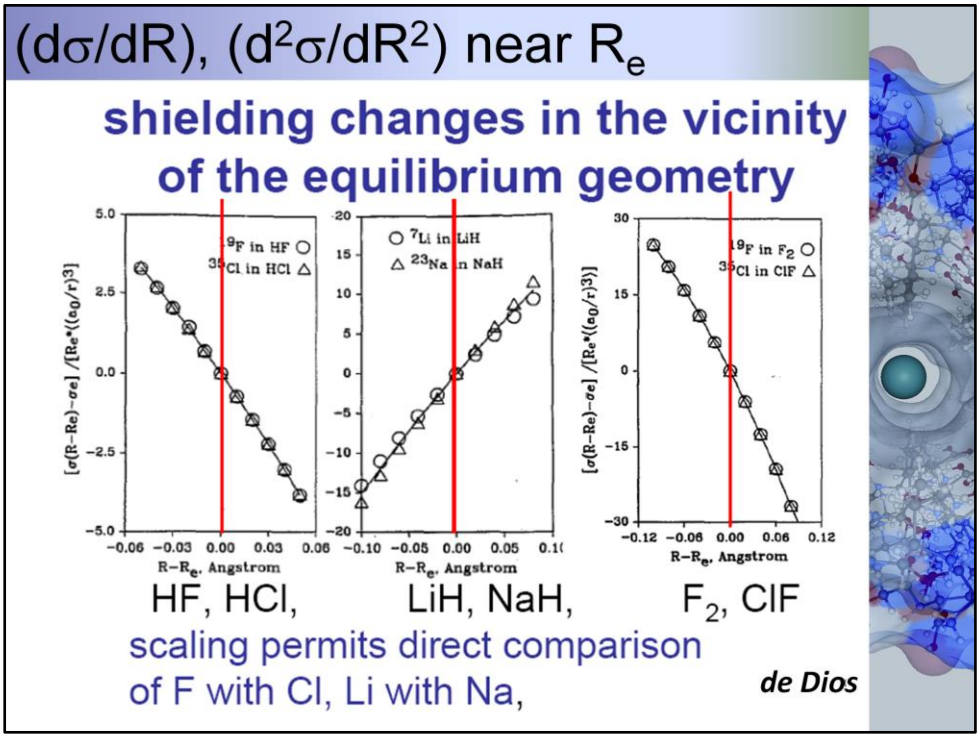
in the vicinity of the equilibrium geometry

proton becomes less shielded with increasing bond length

de Dios

^{23}Na becomes more shielded with increasing bond length[8]

The electronic factor: The shielding function for H_2^+ is accurately known from the work of Roger A. Hegstrom [Phys. Rev. A 19, 17 (1979)] because it is a one-electron system. The other functions we calculated ourselves. Note that the change with bond stretching is opposite sign for Na than for H in H_2^+. My student Angel de Dios did all the calculations J Chem Phys 98, 2208-2217 (1993). The change in sign was already noted by Chesnut, who calculated only the first derivatives at Re for various binary diatomics and had no good explanation. THE SHAPE OF THE SHIELDING SURFACE IS THE SAME, only the location of R_e is different.



$(d\sigma/dR)$, $(d^2\sigma/dR^2)$ near R_e

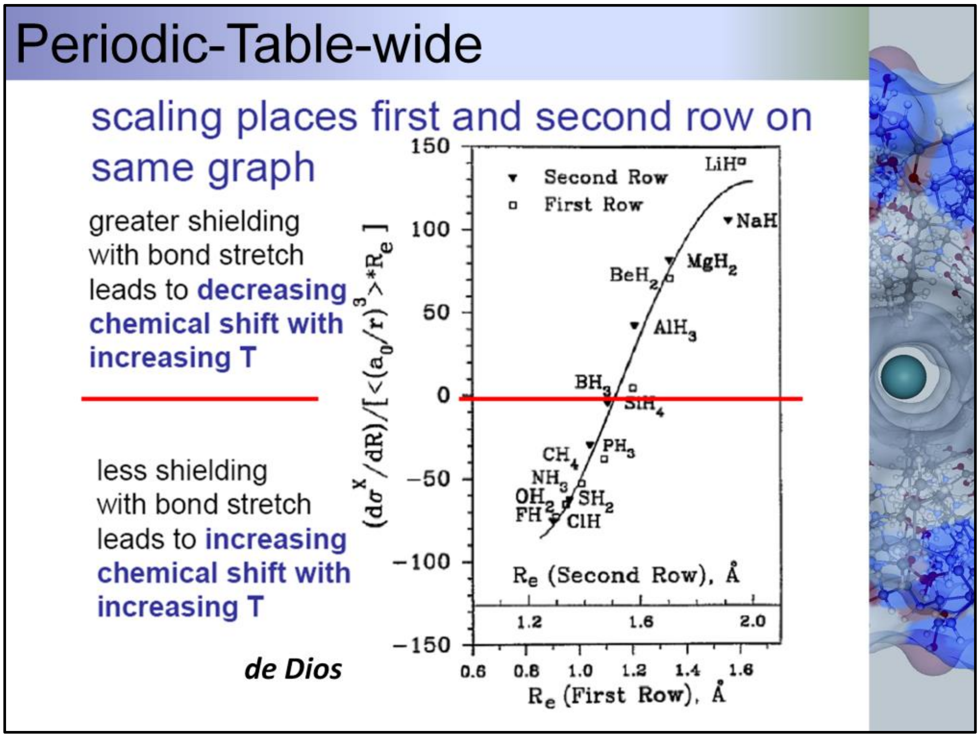
shielding changes in the vicinity of the equilibrium geometry

HF, HCl, LiH, NaH, F_2, ClF

scaling permits direct comparison of F with Cl, Li with Na,

de Dios

Electronic factor scales with $<a_0^3/r^3>$ α . Again $<1/r^3>$! and polarizability



Periodic-Table-wide

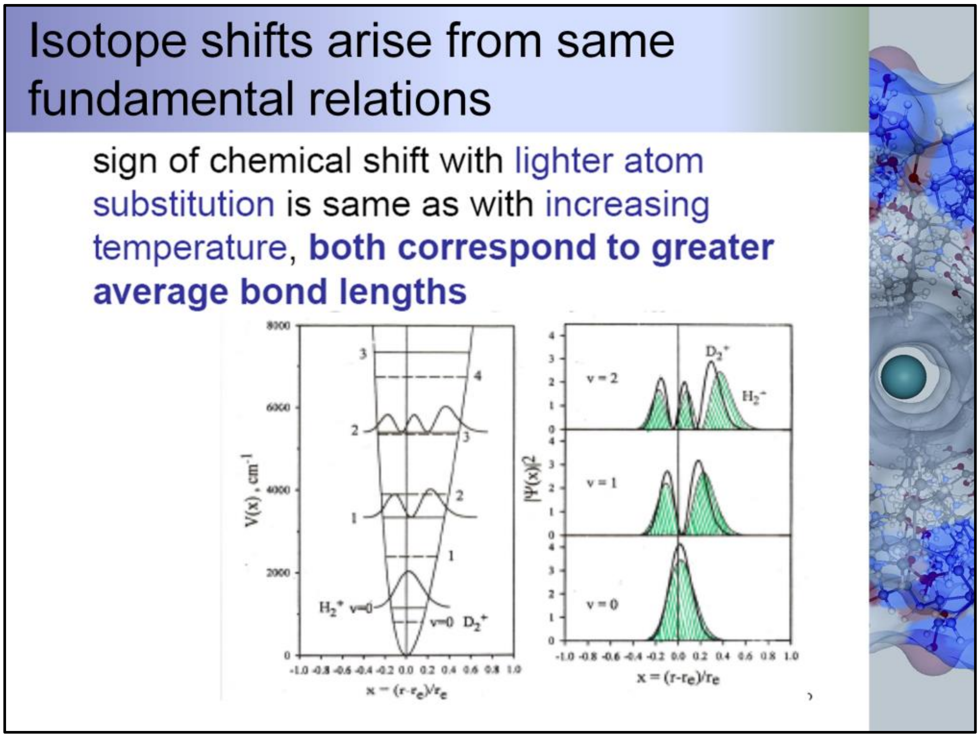
scaling places first and second row on same graph

greater shielding with bond stretch leads to **decreasing chemical shift with increasing T**

less shielding with bond stretch leads to **increasing chemical shift with increasing T**

de Dios

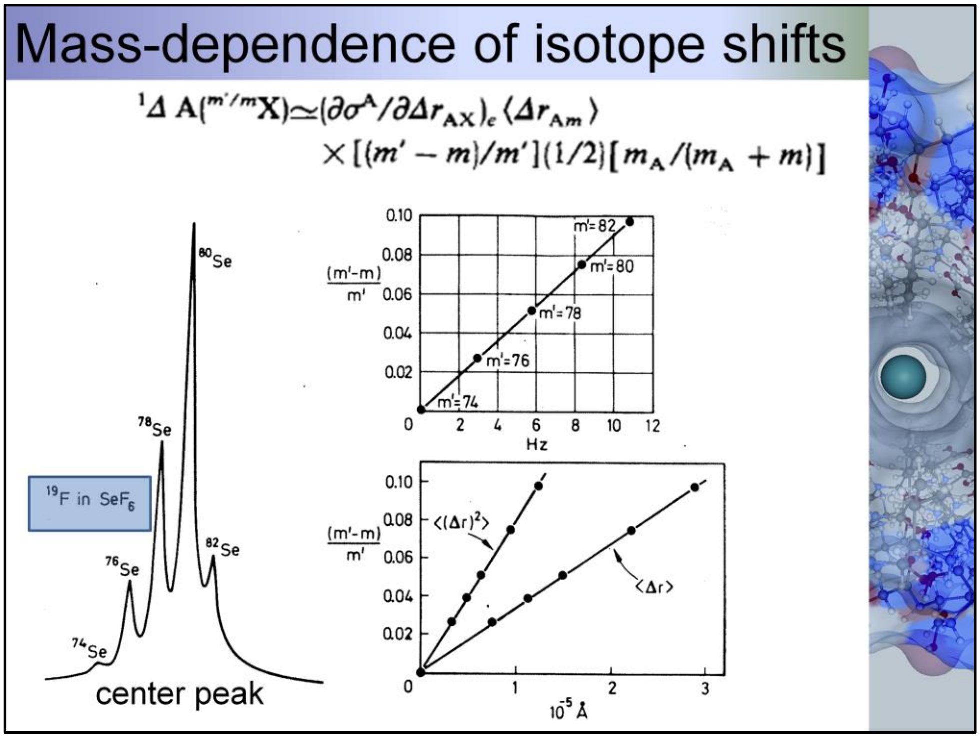
Electronic factor: Proceeding across a row of the Periodic table, at R_e we find the first derivative of the shielding to behave in this way, and the successive rows below do scale to the first long row according to the atomic values $\langle a_0^3/r^3\rangle_{atomic}$ α with scaling of R_e as well.



Isotope shifts arise from same fundamental relations

sign of chemical shift with lighter atom substitution is same as with increasing temperature, **both correspond to greater average bond lengths**

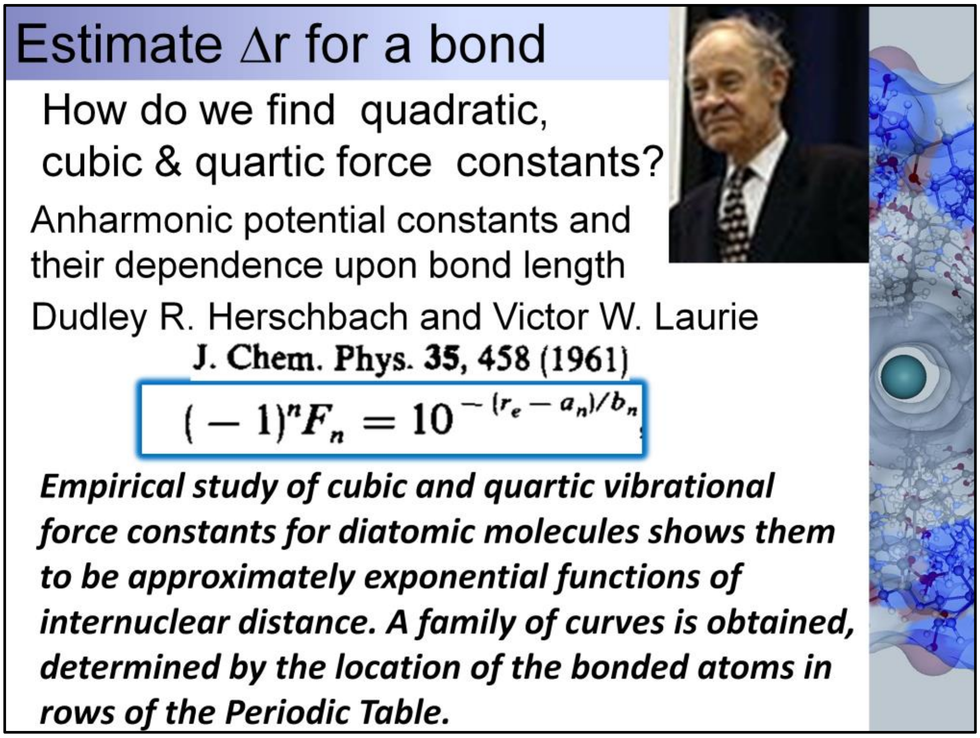
(electronic factor)(dynamic factor) Protons in green undergo greater excursions away from equilibrium than the heavier deuterium. Using these vibrational functions to carry out the averages, we find the sign of the isotope shift and also the additive nature of the isotope shift.



Mass-dependence of isotope shifts

$$^{1}\Delta\,A(^{m'/m}X)\simeq(\partial\sigma^{A}/\partial\Delta r_{AX})_{e}\langle\Delta r_{Am}\rangle \times[(m'-m)/m'](1/2)[m_{A}/(m_{A}+m)]$$

Isotope shifts are the product of two parts: a mass-independent electronic factor (shielding derivatives) and a mass-dependent dynamic factor. **Mass-dependent dynamic factor:** We were able to show that the isotope shift upon substitution of m with m' is proportional to (m'-m)/m' where in the case of Se-induced F-19 shifts, m' can be 74 or 76 or 78 or 80 or 82 in comparison to Se-77 which is spin ½ and gives the doublet 1420 Hz apart. The center peak is shown here with well resolved isotope shifts. The mass-dependence of the isotope shifts arise from the mass dependence of the averages of the bond displacement and the mean square displacement. We measured and calculated many isotope shifts including $[Nb(^{12}C^{16}O)_{6-n}(^{13}CO)_n]^-$ and $[Nb(^{12}C^{16}O)_{6-n}(C^{18}O)_n]^-$ ions, in which case we had to derive the general $M(XY)_6$ vibrational coordinates and determine the vibrational functions and find the mass-dependent frequencies. Vibrational frequencies enter into the calculation in the form of cosh functions.



Estimate Δr for a bond

How do we find quadratic, cubic & quartic force constants?

Anharmonic potential constants and their dependence upon bond length

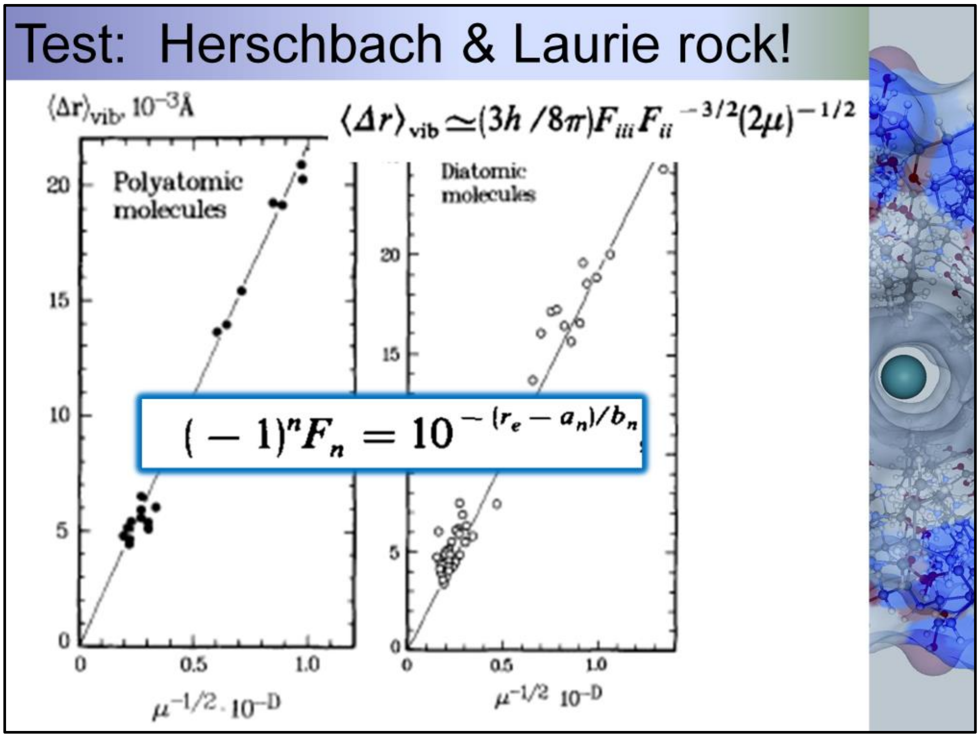
Dudley R. Herschbach and Victor W. Laurie

J. Chem. Phys. **35**, 458 (1961)

$$\boxed{(-1)^n F_n = 10^{-(r_e - a_n)/b_n}}$$

Empirical study of cubic and quartic vibrational force constants for diatomic molecules shows them to be approximately exponential functions of internuclear distance. A family of curves is obtained, determined by the location of the bonded atoms in rows of the Periodic Table.

We have the explicit mass-dependence, we just need **anharmonic force constants**. Everything good happened in early 1960s! Herschbach (then a young Asst Prof. at Harvard) and Laurie found that quadratic, cubic, and quartic vibrational force constants for diatomic molecules are approximately exponential functions of internuclear distance, described by a family of curves which are determined by the location of the bonded atoms in rows of the Periodic Table. And they provided the best fit parameters for these $(-1)^n F_n = 10$ – $\{(r_e-a_n)/b_n\}$

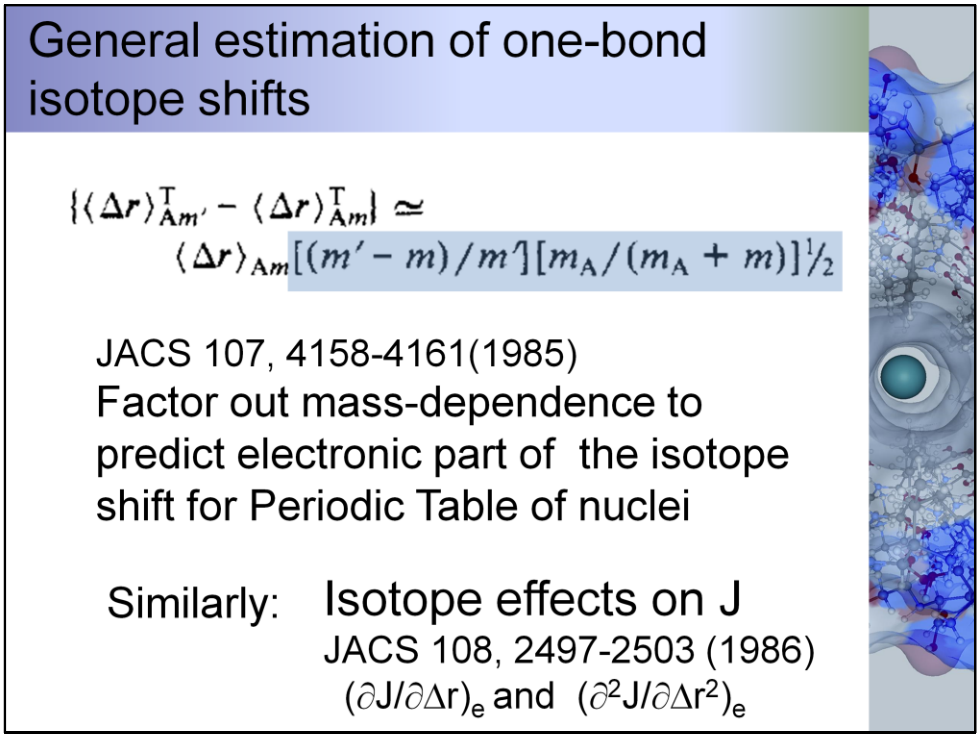


Test: Herschbach & Laurie rock!

$$\langle \Delta r\rangle_{\text{vib}} \simeq (3h/8\pi)F_{iii}F_{ii}{}^{-3/2}(2\mu)^{-1/2}$$

$$(-1)^n F_n = 10^{-(r_e - a_n)/b_n}$$

D is {r_e – a_3/b_3 – [3(r_e-a_2)]/[2b_2] Test of using H&L parms a_n and b_n against actually calculating correct Δr from spectroscopic constants for diatomic molecules and for a set of polyatomic molecules using the best available force fields. H&L rock! Therefore could give reduced isotope shifts (masses not included) for entire Periodic Table. When our undergraduates invited Dudley Herschbach to UIC to give a talk, he graciously accepted. When we met, he said he liked very much that I could do something useful with that little exercise he and his pal from grad student days did in 1961.



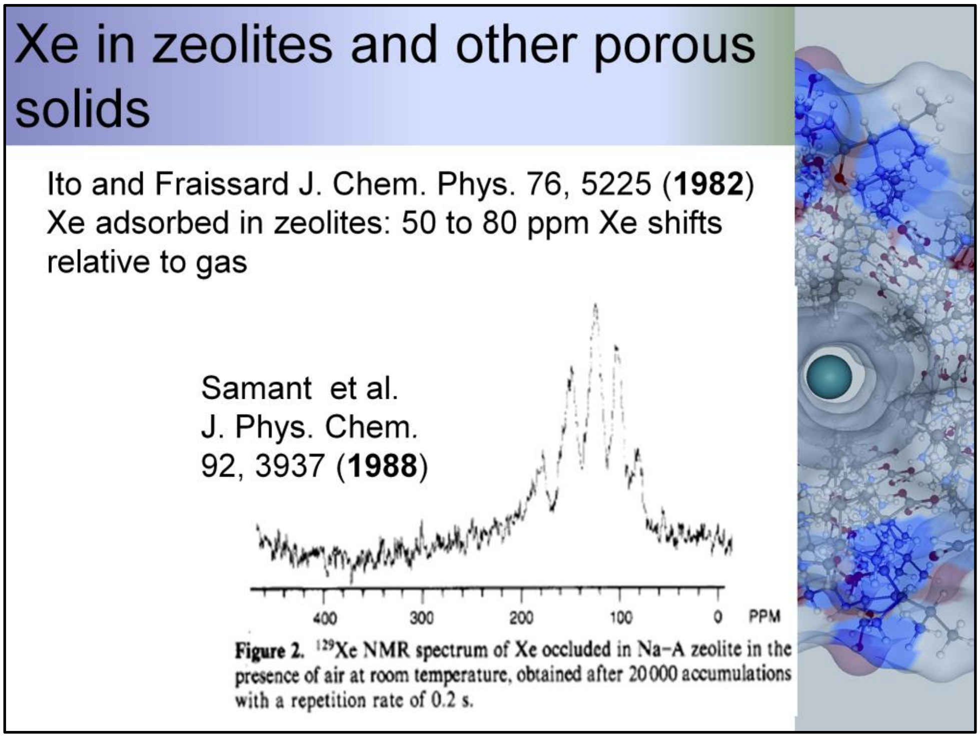
General estimation of one-bond isotope shifts

$$\{\langle\Delta r\rangle^{T}_{Am'} - \langle\Delta r\rangle^{T}_{Am}\} \simeq \langle\Delta r\rangle_{Am}[(m'-m)/m'][m_A/(m_A+m)]^{1/2}$$

JACS 107, 4158-4161(1985)
Factor out mass-dependence to predict electronic part of the isotope shift for Periodic Table of nuclei

Similarly: Isotope effects on J
JACS 108, 2497-2503 (1986)
$(\partial J/\partial\Delta r)_e$ and $(\partial^2 J/\partial\Delta r^2)_e$

Using a simple model I worked out the mass dependence, the highlighted factor is later found to be quite general.



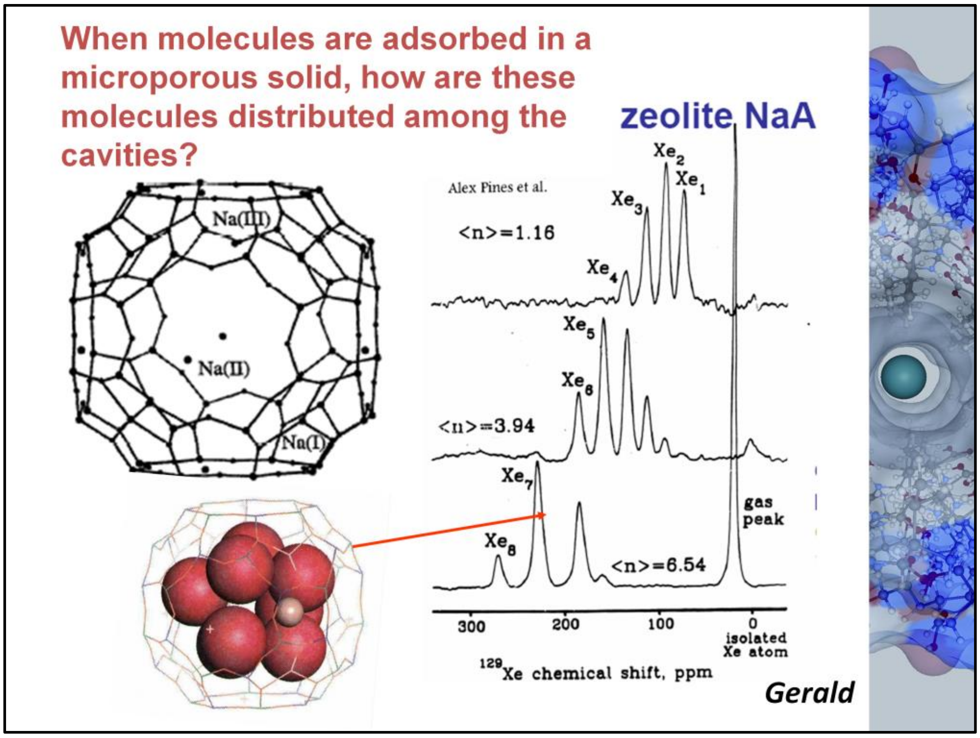
Xe in zeolites and other porous solids

Ito and Fraissard J. Chem. Phys. 76, 5225 (**1982**)
Xe adsorbed in zeolites: 50 to 80 ppm Xe shifts relative to gas

Samant et al.
J. Phys. Chem.
92, 3937 (**1988**)

Figure 2. ^{129}Xe NMR spectrum of Xe occluded in Na–A zeolite in the presence of air at room temperature, obtained after 20000 accumulations with a repetition rate of 0.2 s.

At this time we were busy with isotope shifts, temperature dependence for isolated molecules, and then spin relaxation in the gas phase for a few years and calculations of intermolecular shielding. We had paid no attention to the body of work where Xe is introduced to all types of porous solids starting from 1982, except that we tried to do a few simple things with large internal surfaces like silica gel and quickly decided that was not sufficiently interesting to do because interpretation was a mess, ill defined systems, too many variables, not my style. In fact, I did not look into it until Rex Gerald came to grad school at UIC in Fall 1988. Samant et al. paper came out in June 1988, Rex got interested in working on zeolites because he had been at Amoco with Joe Ray and Mike Munowitz. When I saw the multiple peaks I was hooked. Here was something that could possibly be interpreted. And we understood Xe-other intermolecular shifts. We were well into it when I went to NSF in Fall 1990. But like anything else, we do not want to publish until we already understand our system.

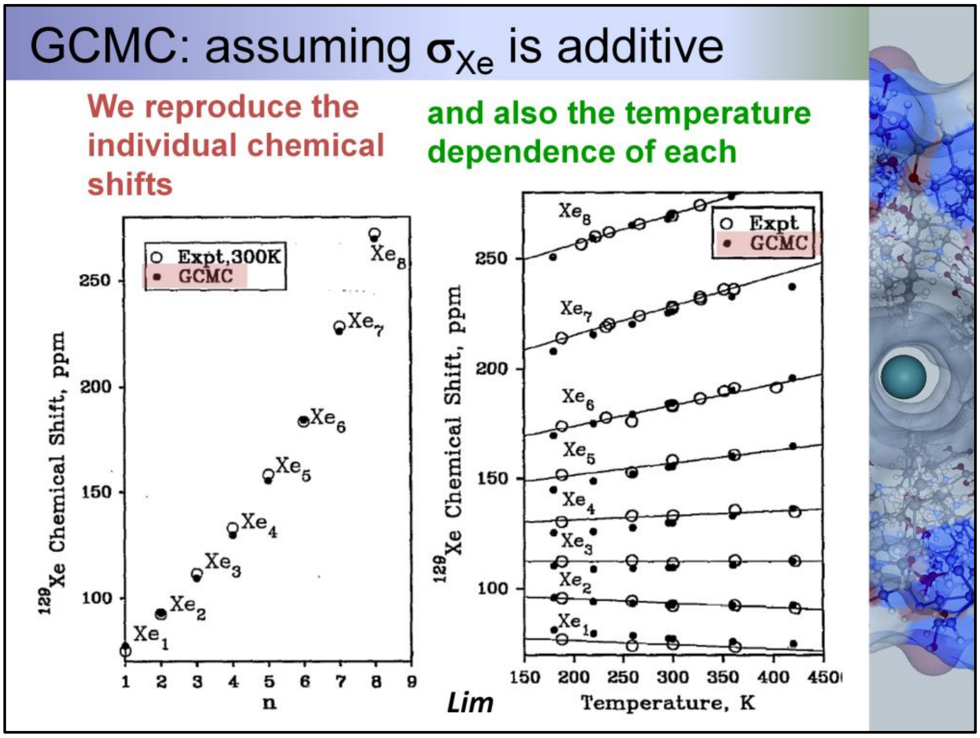


When molecules are adsorbed in a microporous solid, how are these molecules distributed among the cavities?

zeolite NaA

Gerald

We scrupulously eliminated O2 from our samples because we had already done Xe in O2 chemical shifts in 1975 and knew how large and T-dependent that was. We also made sure we had very good zeolite because we wanted no problems with impurities in the solid (any bit of Ca causes the cages to be no longer identical). We were doing a quantitative determination of the distributions and chemical shifts at different temperatures. At this point Feb 1991, Alex Pines published a Phys. Rev. Lett. [B. F. Chmelka, D. Raftery, A. V. McCormick, L. C. de Menorval, R. D. Levine and A. Pines, Phys. Rev. Lett., 1991, 66, 580.] We did not even know Alex was working on Xe let alone zeolites! Rex was devastated to have been scooped. I said, Rex, if you are going to be scooped, it might as well be by Alex Pines and in Phys. Rev. Letters. We did the first systematic study of T dependence of the distribution and also the chemical shifts, we did several Xe loadings and observed as many as 8 in a cage, we presented our results in a poster at Amoco in October 1991 and finally published in 1992. We showed that various simple models suggested by the Pines paper did not fit well enough the distribution that we observed.



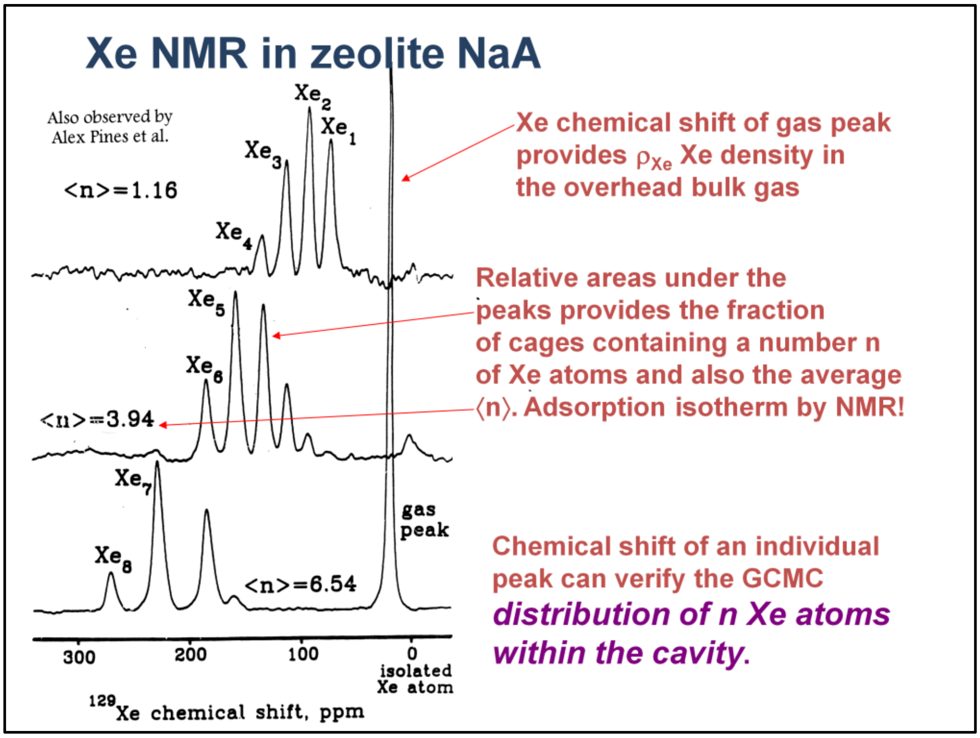
GCMC: assuming σ_{Xe} is additive

We reproduce the individual chemical shifts

and also the temperature dependence of each

Lim

It was not till March 1993 that we could present in 2 conferences a quantitative interpretation of our results by using grand canonical Monte Carlo simulations, and published in April 1994. I thought the easiest way for me to learn how to do that for our system was to visit John Rowlinson. In 1989, John Rowlinson and GB Woods published computer simulations of fluids in zeolites X and Y, in which they used GCMC. I wrote to him out of the blue and asked if I could work with his grad student and learn how to do these types of simulations. He was going to retire and the student was going to graduate by the summer of 1993, so I had to come earlier, if possible. So I spent all of December 1992 (between semesters) in Oxford and wrote my code and ran it. I knew I could not use LJ potentials which everyone was using for Xe, so it was fortunate that in Oxford was E. Brian Smith who told me about the Maitland-Smith potential that did not cost more time than LJ. I came back again in March 1993 to attend a conference honoring Rowlinson and it was lucky I did because the graduate student was simulating mixtures of methane and nitrogen and I was already thinking that we could do studies of competitive adsorption. Of course, we needed shielding surfaces and we could not do Xe calculations at that time, so we were doing Ar and scaling to Xe. NMR people were having fun with us, they said Cynthia is the only one doing Ar NMR. For the shielding function of Ar in zeolite cage, we had to do fragments of the cage and approach the Ar along trajectories in various directions perpendicular to the different types of aluminosilicate rings. We scaled Ar-Ar to Xe-Xe, which we had already tested against our gas phase work. Angel had already shown in 1992 the additivity of Ar shielding in Ar3 linear and triangular, so I took the leap of faith and made the additivity assumption: at any one position, a Xe nucleus has a total isotropic shielding that could be found by summing together the shielding contributions from various cage atoms and other Xe atoms in the same cage.



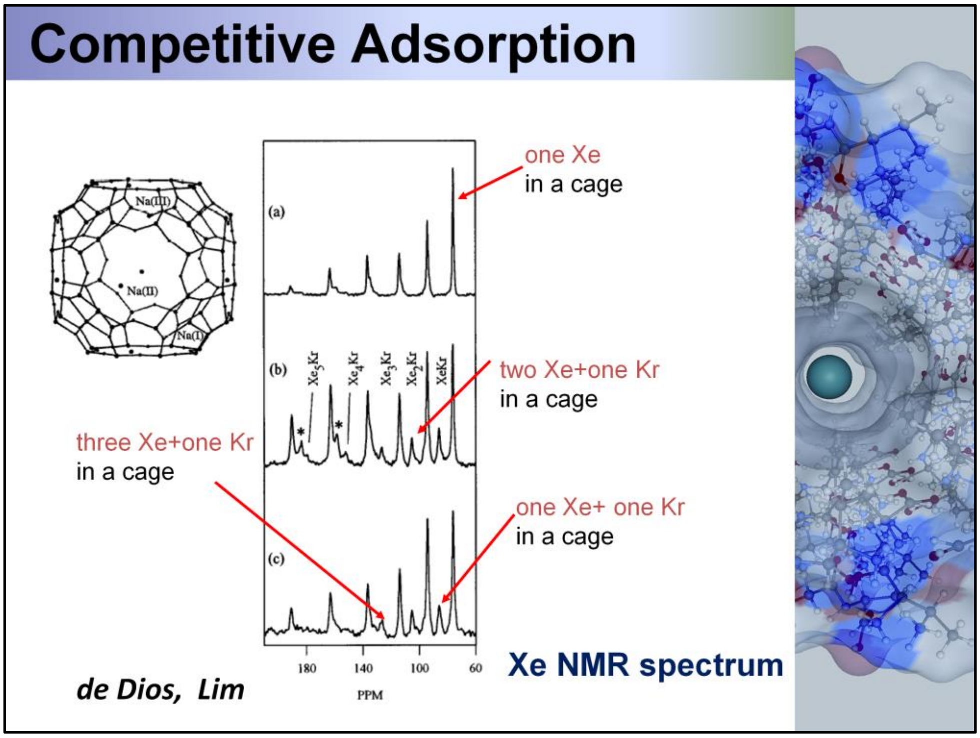
Xe NMR in zeolite NaA

Xe chemical shift of gas peak provides ρ_{Xe} Xe density in the overhead bulk gas

Relative areas under the peaks provides the fraction of cages containing a number n of Xe atoms and also the average ⟨n⟩. Adsorption isotherm by NMR!

Chemical shift of an individual peak can verify the GCMC ***distribution of n Xe atoms within the cavity***.

So, from the 129Xe NMR spectrum we not only can obtain the average chemical shift of n Xe atoms in a cage, we can also get from the relative intensities the fraction of cages that have exactly n Xe atoms as well as <n>, the average number of Xe atoms within the zeolite. And because we calibrated our volume and counted out our number of Xe atoms in making the sealed sample, we could also find the Xe density in the overhead bulk gas, even when we can not see the gas peak. Thus, we have the experimental adsorption isotherm of Xe via NMR. The experimental chemical shift of n Xe atoms in a cage can be used to test the chemical shift calculations that are found in our GCMC simulations. Agreement means that our GCMC is providing the correct one and two-body distribution functions for Xe in the cage.



Competitive Adsorption

one Xe
in a cage

two Xe+one Kr
in a cage

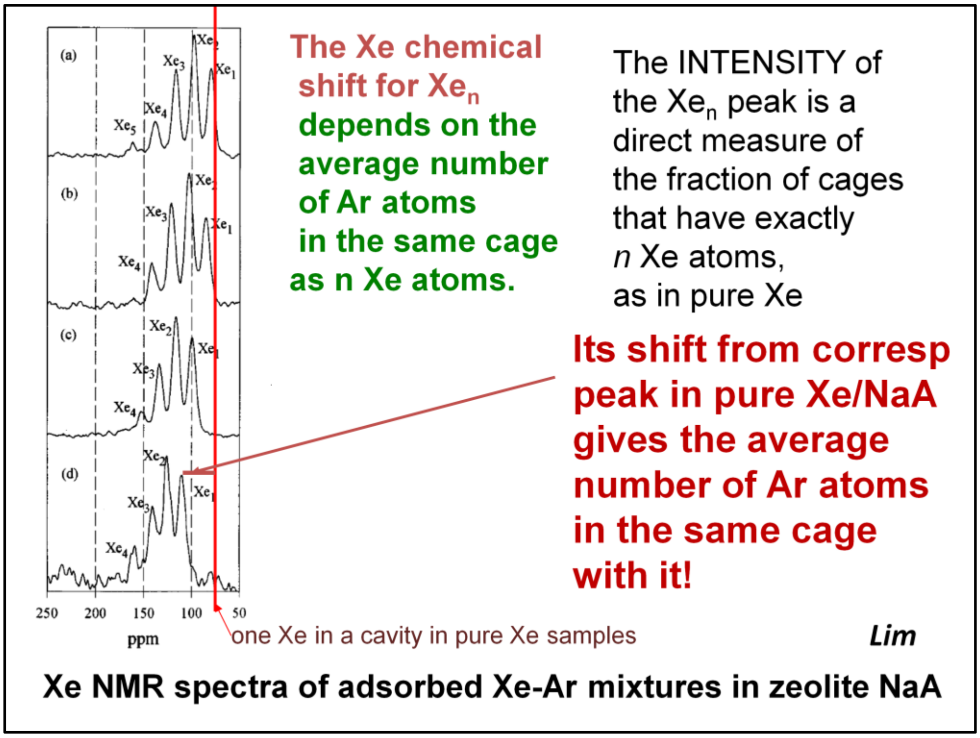
three Xe+one Kr
in a cage

one Xe+ one Kr
in a cage

Xe NMR spectrum

de Dios, Lim

We get as detailed a description of competitive adsorption as is possible. In this case we can see the chemical shifts and the distributions for 2 Xe + 1Kr, 1Xe and 1Kr, etc. in a cage.



The Xe chemical shift for Xe_n depends on the average number of Ar atoms in the same cage as n Xe atoms.

The INTENSITY of the Xe_n peak is a direct measure of the fraction of cages that have exactly *n* Xe atoms, as in pure Xe

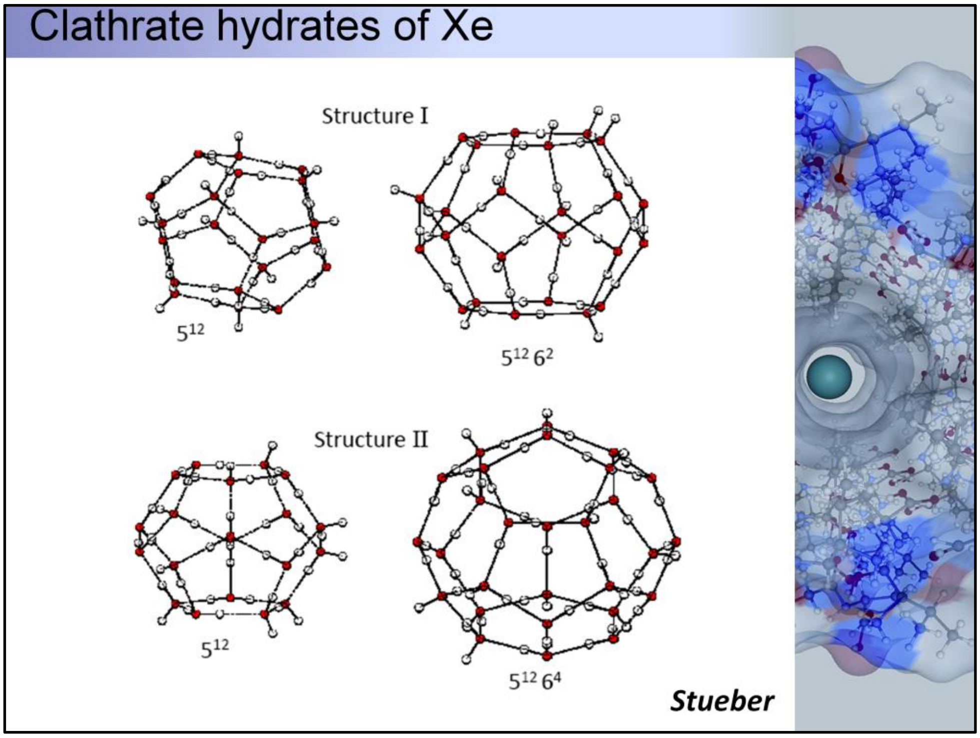
Its shift from corresp peak in pure Xe/NaA gives the average number of Ar atoms in the same cage with it!

one Xe in a cavity in pure Xe samples

Lim

Xe NMR spectra of adsorbed Xe-Ar mixtures in zeolite NaA

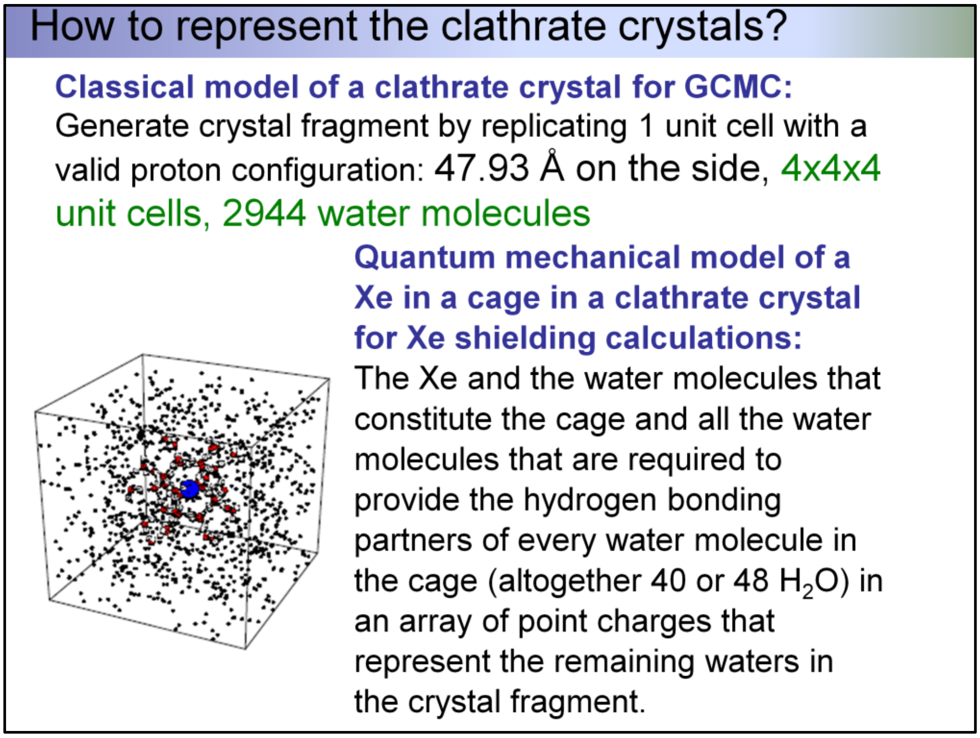
Where the other molecule is free to move from one cage to another, we still get a detailed picture of competitive adsorption. For any mole fractions in the overhead gas, we can get from Xe shifts alone, the <m>, average number of Ar atoms in the same cage as n Xe atoms! Again the relative intensities provide us with the distribution of Xe among the cages.



Clathrate hydrates of Xe

Stueber

Water crystallizes around Xe atoms as templates. Two of the clathrate hydrates are shown here. Structure I and Structure two. Each has small and large cages.

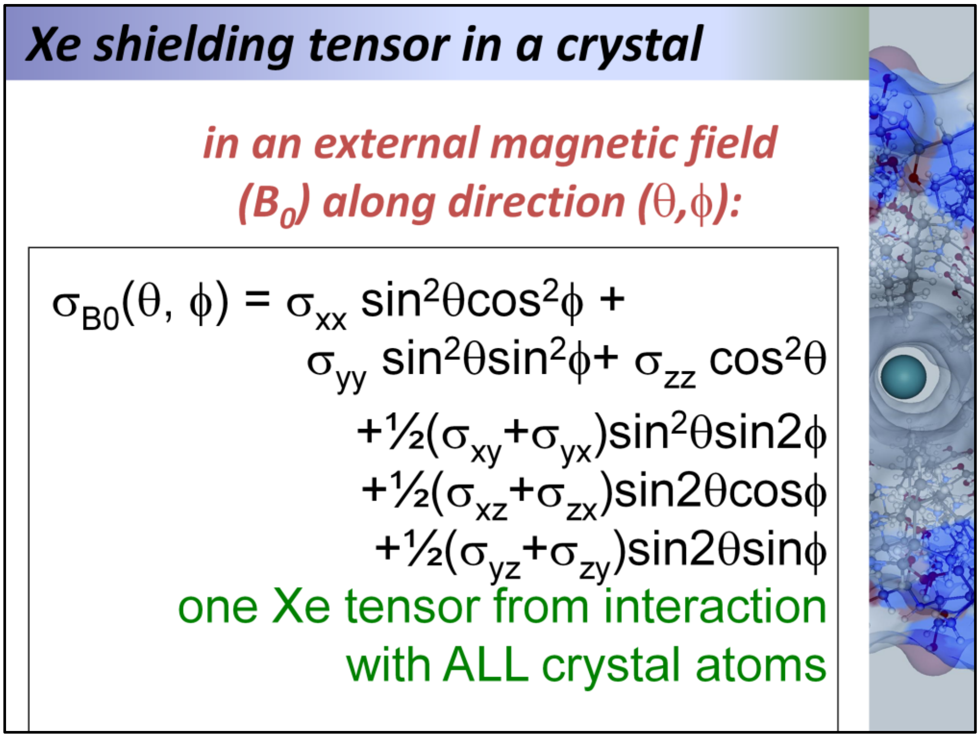


How to represent the clathrate crystals?

Classical model of a clathrate crystal for GCMC:
Generate crystal fragment by replicating 1 unit cell with a valid proton configuration: 47.93 Å on the side, 4x4x4 unit cells, 2944 water molecules

Quantum mechanical model of a Xe in a cage in a clathrate crystal for Xe shielding calculations:
The Xe and the water molecules that constitute the cage and all the water molecules that are required to provide the hydrogen bonding partners of every water molecule in the cage (altogether 40 or 48 H_2O) in an array of point charges that represent the remaining waters in the crystal fragment.

To represent the clathrate crystals in the computer is not trivial, particular attention has to be paid to the disorder of the H atoms and still follow the ice rules. We did a very large number of calculations of Xe at various positions in the small and also the larger cage in the clathrate.



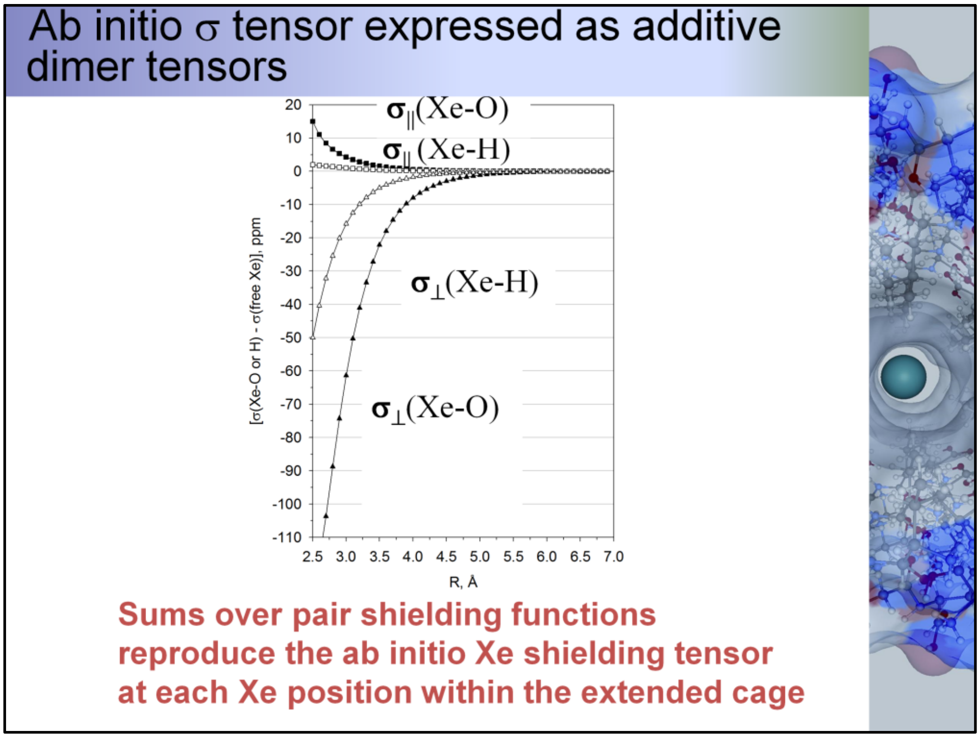
Xe shielding tensor in a crystal

in an external magnetic field (B_0) along direction (θ,ϕ):

$$\sigma_{B0}(\theta, \phi) = \sigma_{xx}\sin^2\theta\cos^2\phi + \sigma_{yy}\sin^2\theta\sin^2\phi + \sigma_{zz}\cos^2\theta + \tfrac{1}{2}(\sigma_{xy}+\sigma_{yx})\sin^2\theta\sin 2\phi + \tfrac{1}{2}(\sigma_{xz}+\sigma_{zx})\sin 2\theta\cos\phi + \tfrac{1}{2}(\sigma_{yz}+\sigma_{zy})\sin 2\theta\sin\phi$$

one Xe tensor from interaction with ALL crystal atoms

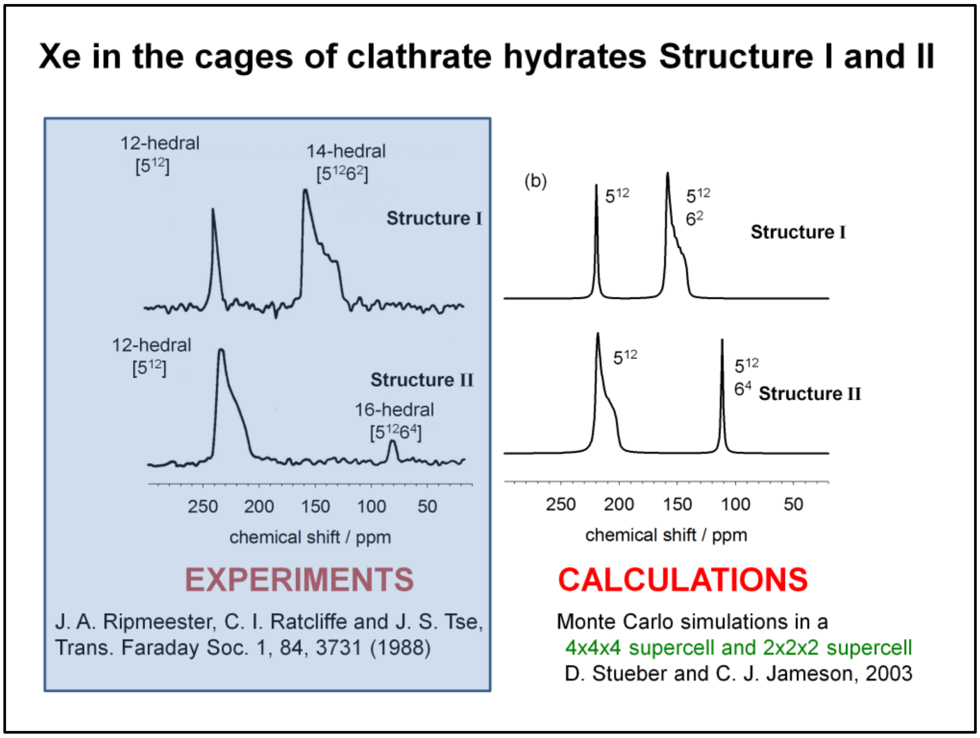
Now we need to get σ_{XX} ab initio for each Xe position in the cage



Ab initio σ tensor expressed as additive dimer tensors

Sums over pair shielding functions reproduce the ab initio Xe shielding tensor at each Xe position within the extended cage

At a specific position in the cage the ab initio σ tensor of Xe is mathematically expressed as a summation of these four functions over all O and all H atoms in the system.



Xe in the cages of clathrate hydrates Structure I and II

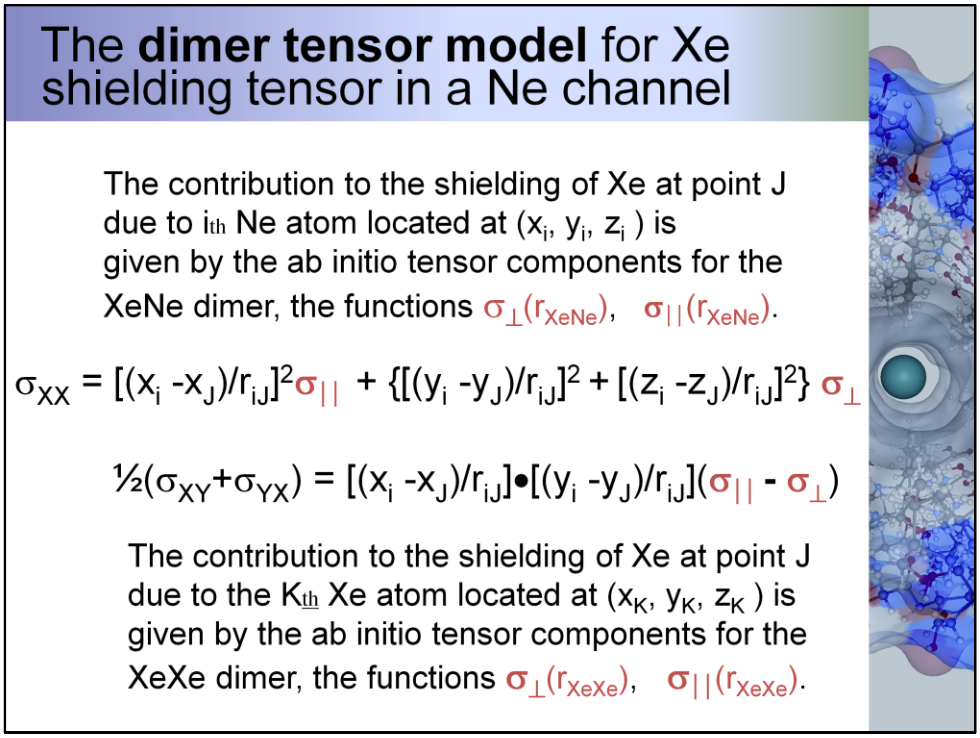
EXPERIMENTS

J. A. Ripmeester, C. I. Ratcliffe and J. S. Tse, Trans. Faraday Soc. 1, 84, 3731 (1988)

CALCULATIONS

Monte Carlo simulations in a
4x4x4 supercell and 2x2x2 supercell
D. Stueber and C. J. Jameson, 2003

Beyond these, we also reproduced tensors for several other clathrate hydrate structures (not shown in this talk)



The **dimer tensor model** for Xe shielding tensor in a Ne channel

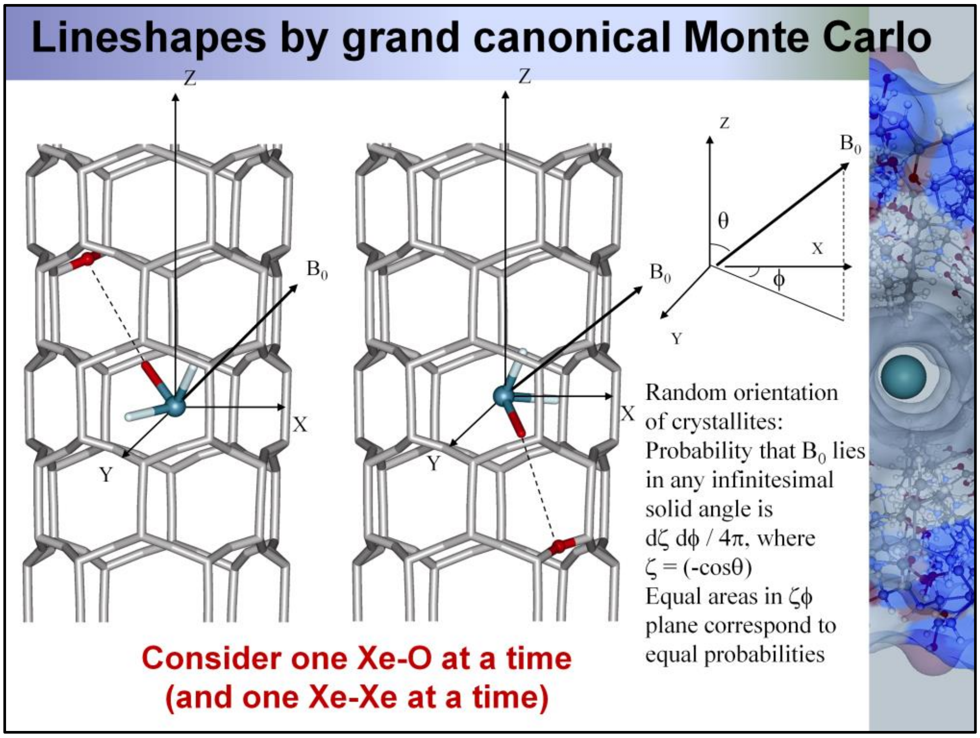
The contribution to the shielding of Xe at point J due to ith Ne atom located at (x_i, y_i, z_i) is given by the ab initio tensor components for the XeNe dimer, the functions $\sigma_{\perp}(r_{XeNe})$, $\sigma_{||}(r_{XeNe})$.

$$\sigma_{XX} = [(x_i - x_J)/r_{iJ}]^2 \sigma_{||} + \{[(y_i - y_J)/r_{iJ}]^2 + [(z_i - z_J)/r_{iJ}]^2\} \sigma_{\perp}$$

$$\tfrac{1}{2}(\sigma_{XY}+\sigma_{YX}) = [(x_i - x_J)/r_{iJ}]\bullet[(y_i - y_J)/r_{iJ}](\sigma_{||} - \sigma_{\perp})$$

The contribution to the shielding of Xe at point J due to the Kth Xe atom located at (x_K, y_K, z_K) is given by the ab initio tensor components for the XeXe dimer, the functions $\sigma_{\perp}(r_{XeXe})$, $\sigma_{||}(r_{XeXe})$.

This is how I made use of additivity to get the contributions to the individual shielding tensor components

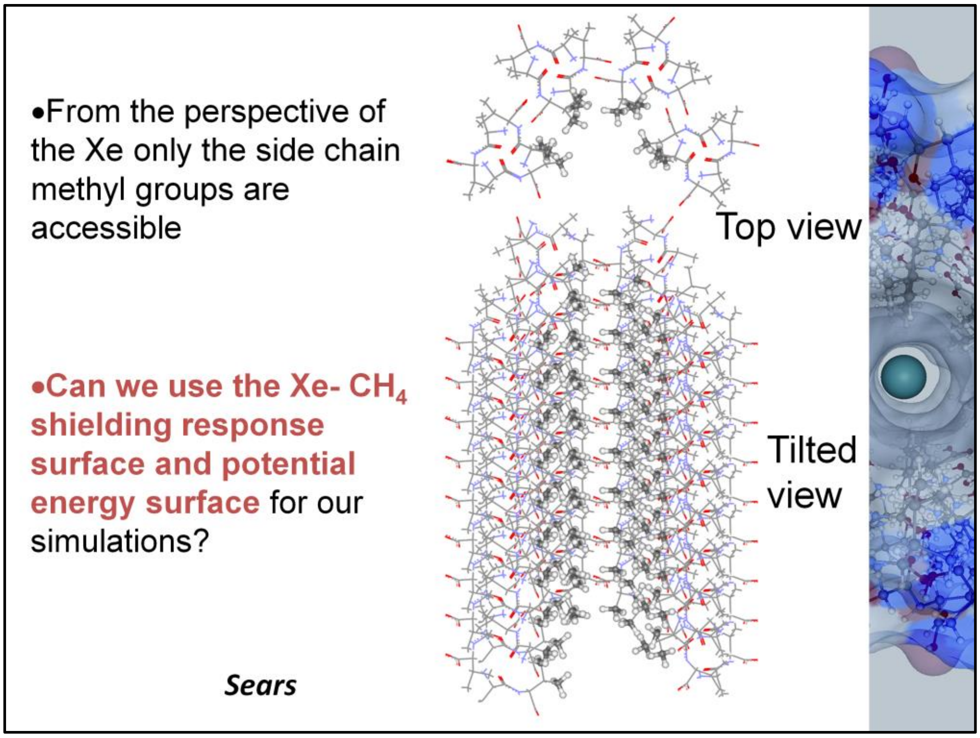


Lineshapes by grand canonical Monte Carlo

Random orientation of crystallites: Probability that B_0 lies in any infinitesimal solid angle is $d\zeta\ d\phi\ /\ 4\pi$, where $\zeta = (-\cos\theta)$ Equal areas in $\zeta\phi$ plane correspond to equal probabilities

Consider one Xe-O at a time (and one Xe-Xe at a time)

Impose the condition that the chemical potential of Xe in the overhead bulk gas is the same as the chemical potential of Xe in the adsorbed phase (decide to create, destroy, displace Xe atoms, accordingly)
Choose a B_0 direction, taking steps of equal probability in $\zeta\phi$ space
Sum tensor components along the B_0 direction from each Xe-O (or other channel atom) pair, and from each Xe-Xe pair.
This approach came very handy when John Ripmeester asked me at the second XeMAT conference (in France, 2003) if I wanted to collaborate on some Xe work they were doing in biological systems. In particular he said they were going to put Xe into two related dipeptide crystals: alanine valine and valyl alanine. Like myself, John liked to work with simple well-defined physical systems, where interpretation of results is possible. I said yes, of course. As soon as I got back from the XeMAT my graduate student Devin Sears downloaded the pdb files for these two dipeptide crystals so we could look at the structure that would be receiving the Xe atoms.

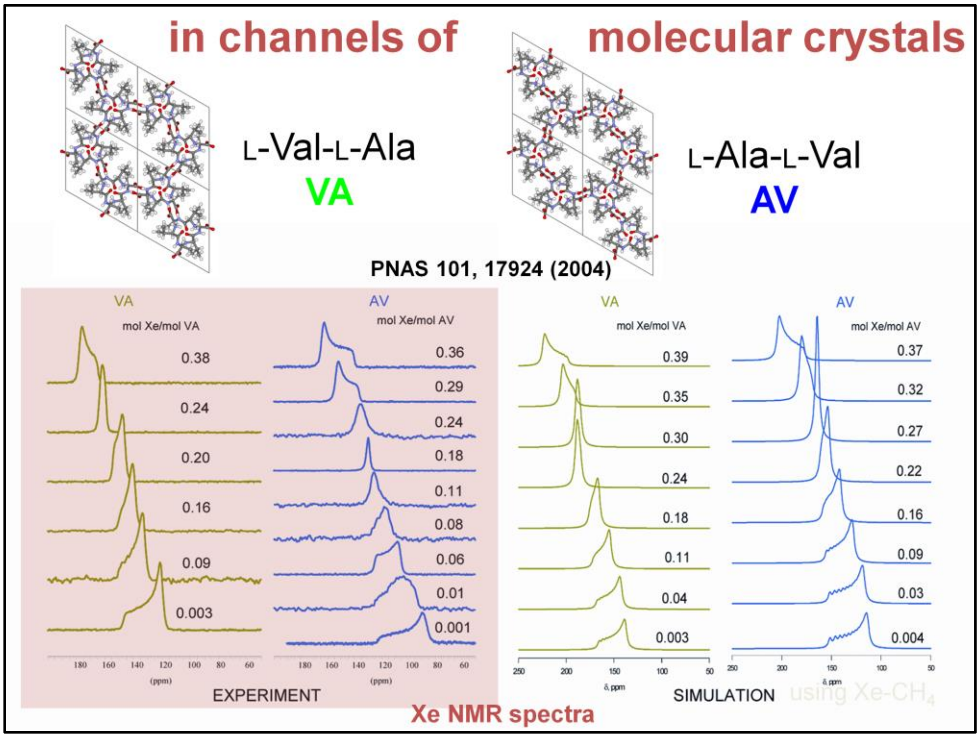


- From the perspective of the Xe only the side chain methyl groups are accessible

- **Can we use the Xe- CH_4 shielding response surface and potential energy surface** for our simulations?

Sears

Can we use our ab initio Xe-CH_4 shielding tensor surface? After all, it appears that the Xe comes in contact only with the CH_3 side chains. Like the Xe-clathrate, we had gazillion points calculated for the ab initio tensor surface for Xe approaching CH_4 molecule; thesevalues we could write in mathematical form in terms of Xe-C and Xe-H dimer tensor contributions.



in channels of molecular crystals

L-Val-L-Ala
VA

L-Ala-L-Val
AV

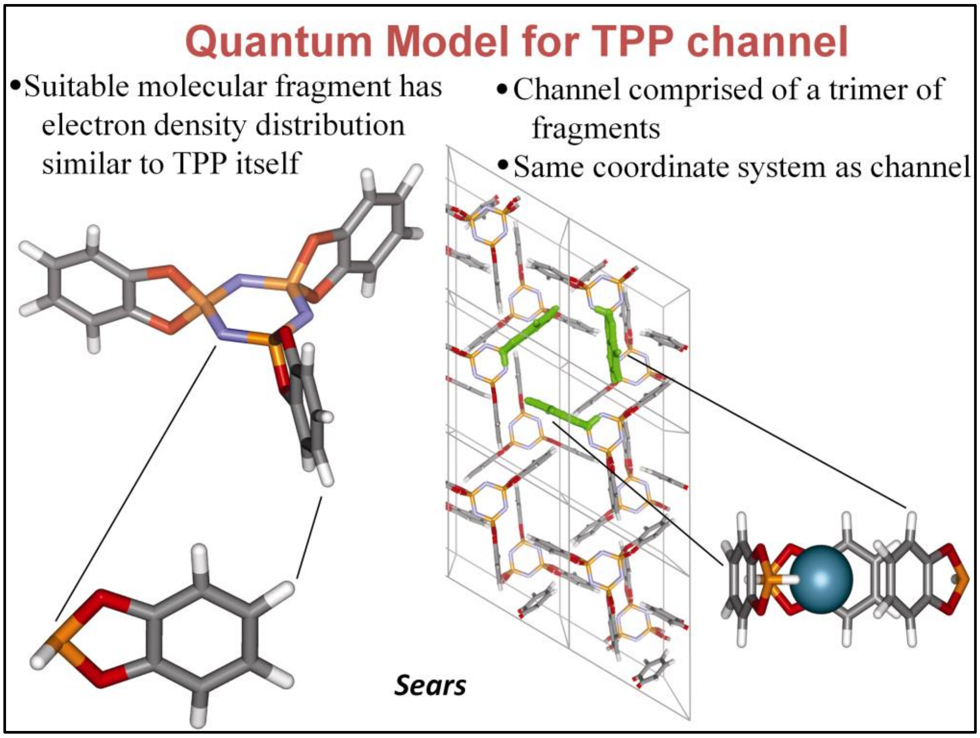
PNAS 101, 17924 (2004)

EXPERIMENT

SIMULATION using Xe-CH_4

Xe NMR spectra

We finished the Grand Canonical Monte Carlo simulations and sent the results via e-mail to Ripmeester and co-workers, to which they replied, “we have just done the experiments and these are our results” by return e-mail. Both our groups were very pleased with the agreement and we published this in PNAS.

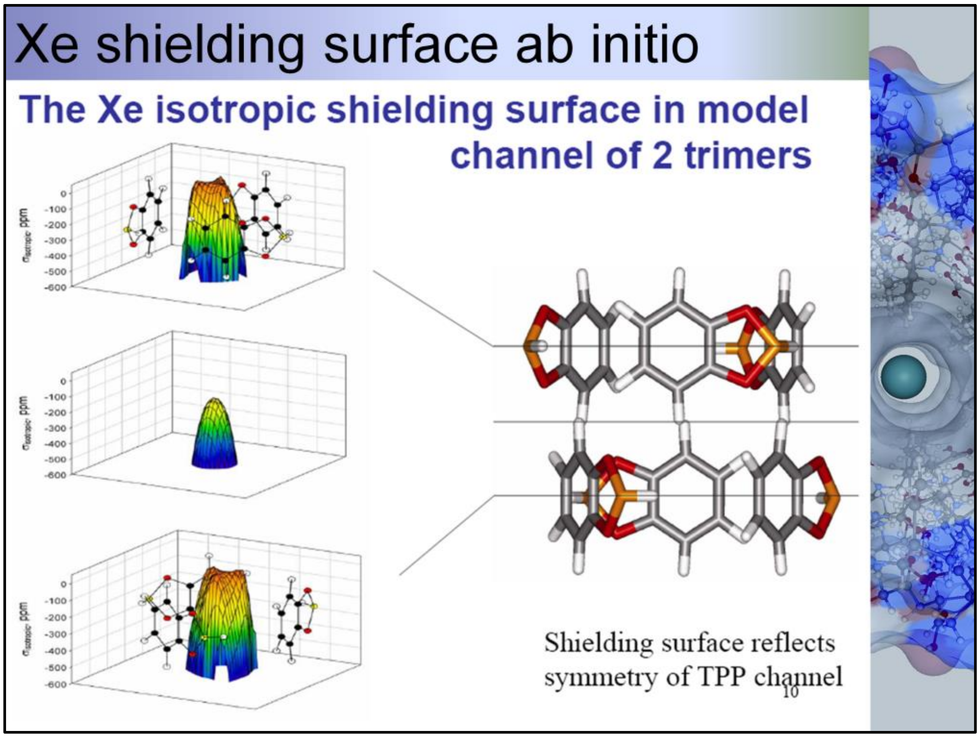


Quantum Model for TPP channel

- Suitable molecular fragment has electron density distribution similar to TPP itself
- Channel comprised of a trimer of fragments
- Same coordinate system as channel

Sears

Another nanochannel which has been explored by Xe atom is the tris(o-phenylenedioxy)cyclotriphosphazene (TPP) crystal, with the periodic structure on the right. We carried out the ab initio calculations of Xe shielding in the presence of a suitable molecular fragment model system.



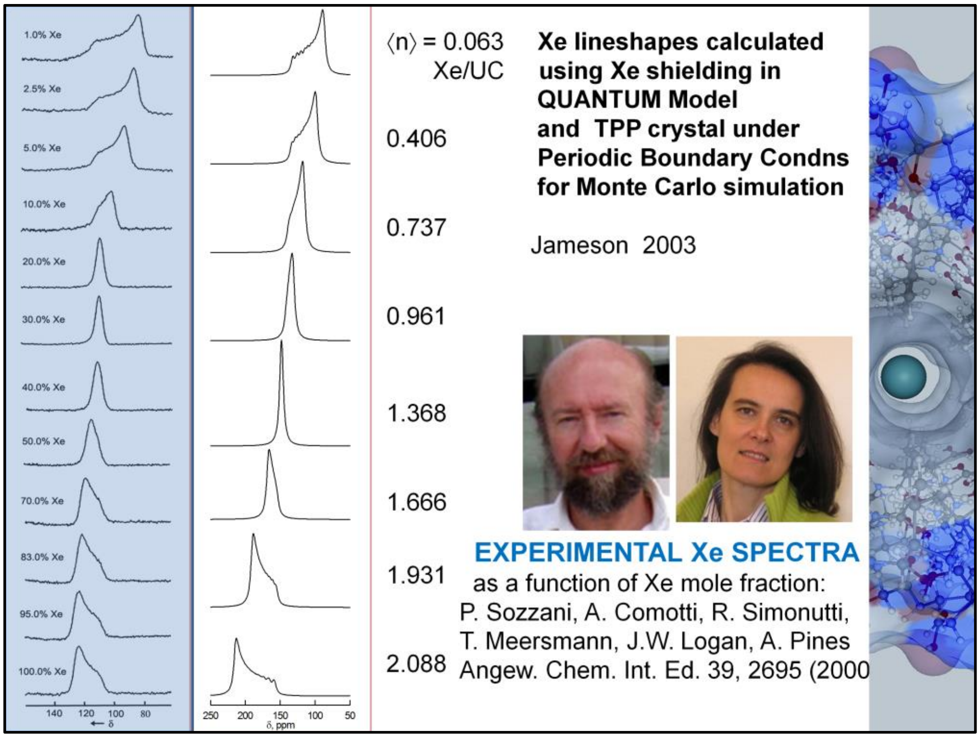
Xe shielding surface ab initio

The Xe isotropic shielding surface in model channel of 2 trimers

Shielding surface reflects symmetry of TPP channel

10

The Xe shielding surfaces in the model channel of 2 trimers consists of a mathematical surface fitted to a very large number of quantum calculations with Xe in various positions within the model channel.



⟨n⟩ = 0.063 Xe/UC

0.406

0.737

0.961

1.368

1.666

1.931

2.088

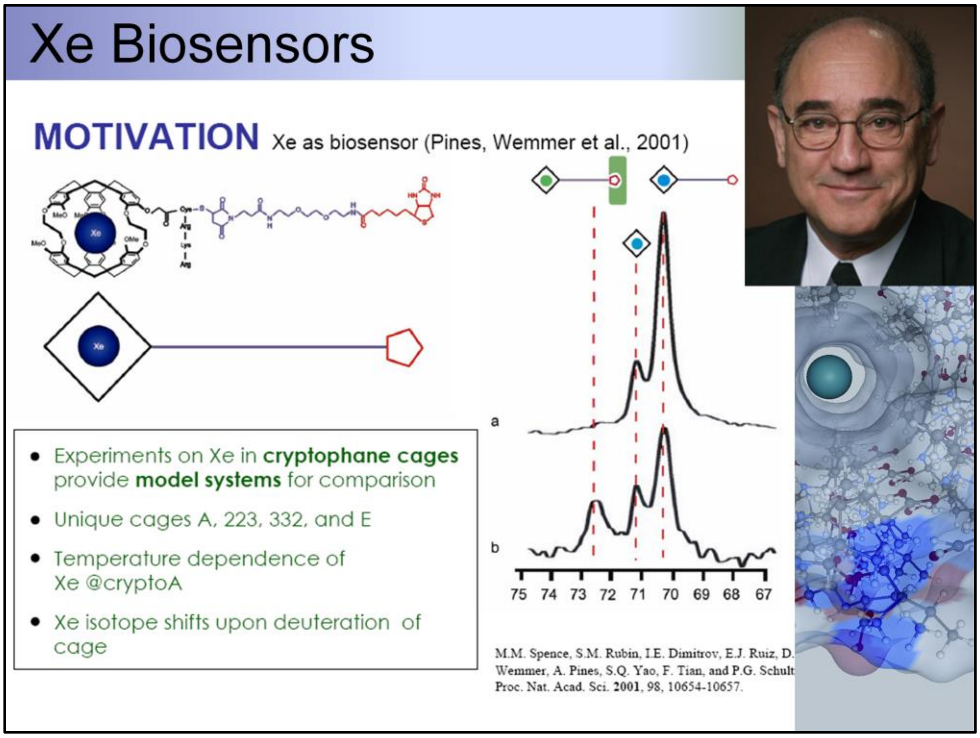
Xe lineshapes calculated using Xe shielding in QUANTUM Model and TPP crystal under Periodic Boundary Condns for Monte Carlo simulation

Jameson 2003

EXPERIMENTAL Xe SPECTRA

as a function of Xe mole fraction:
P. Sozzani, A. Comotti, R. Simonutti,
T. Meersmann, J.W. Logan, A. Pines
Angew. Chem. Int. Ed. 39, 2695 (2000

Here we have our calculated Xe lineshapes which we obtained using the procedure we developed in doing the dipeptide nanochannels, compared with the experimental spectra obtained using hyperpolarized Xe.



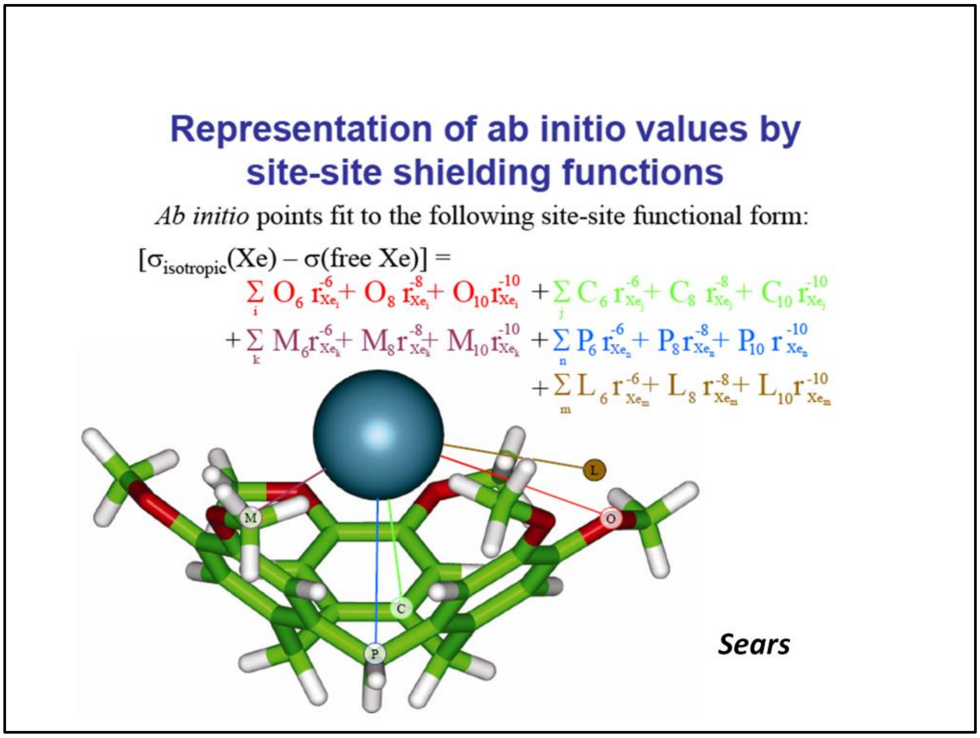
Xe Biosensors

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. Wemmer, A. Pines, S.Q. Yao, F. Tian, and P.G. Schult
Proc. Nat. Acad. Sci. **2001**, 98, 10654-10657.

Alex Pines and his group had been working with David Wemmer on developing a Xe biosensor which takes advantage of the intrinsically large range of Xe atom chemical shifts. An important question is: What is the mechanism of the sensing action?



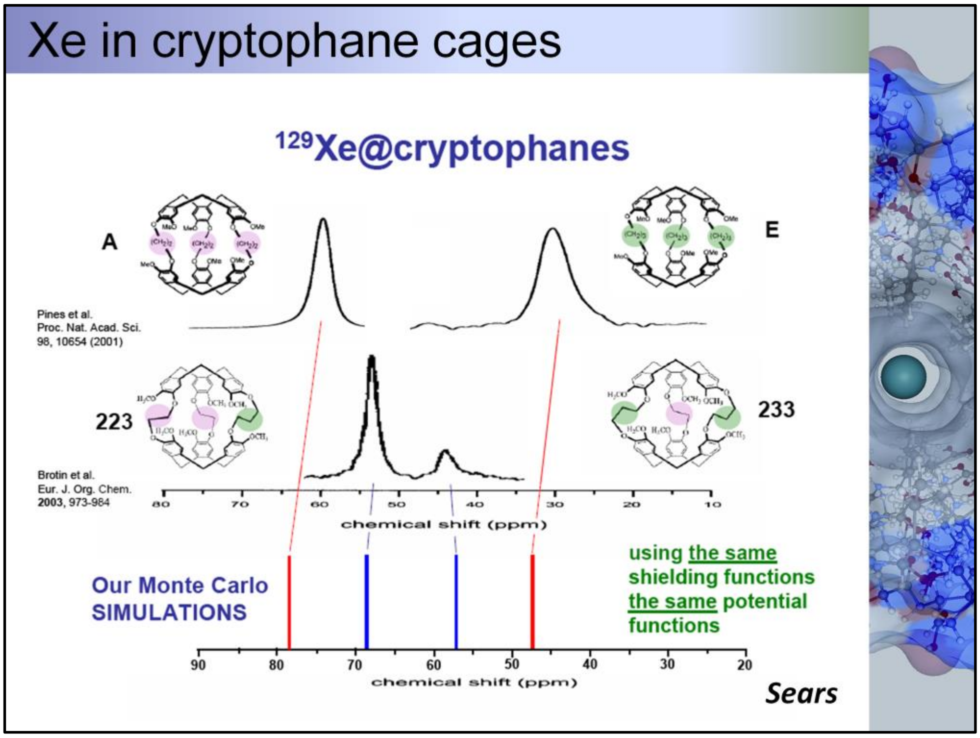
Representation of ab initio values by site-site shielding functions

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

$$[\sigma_{\text{isotropic}}(\text{Xe}) - \sigma(\text{free Xe})] = \sum_i O_6 r_{\text{Xe}_i}^{-6} + O_8 r_{\text{Xe}_i}^{-8} + O_{10} r_{\text{Xe}_i}^{-10} + \sum_j C_6 r_{\text{Xe}_j}^{-6} + C_8 r_{\text{Xe}_j}^{-8} + C_{10} r_{\text{Xe}_j}^{-10}$$
$$+ \sum_k M_6 r_{\text{Xe}_k}^{-6} + M_8 r_{\text{Xe}_k}^{-8} + M_{10} r_{\text{Xe}_k}^{-10} + \sum_n P_6 r_{\text{Xe}_n}^{-6} + P_8 r_{\text{Xe}_n}^{-8} + P_{10} r_{\text{Xe}_n}^{-10}$$
$$+ \sum_m L_6 r_{\text{Xe}_m}^{-6} + L_8 r_{\text{Xe}_m}^{-8} + L_{10} r_{\text{Xe}_m}^{-10}$$

Sears

We could not do ab initio calculations on the full biosensor at the time, but we decided to try and understand the magnitudes of the Xe chemical shifts in the cryptophane cages themselves. We did quantum calculations on Xe in the presence of half the cryptophane-A cage, mapping out the shielding surface by fitting to this mathematical function, which takes into account the different types of atomic and group sites that contribute to Xe intermolecular shielding.



Xe in cryptophane cages

^{129}Xe@cryptophanes

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

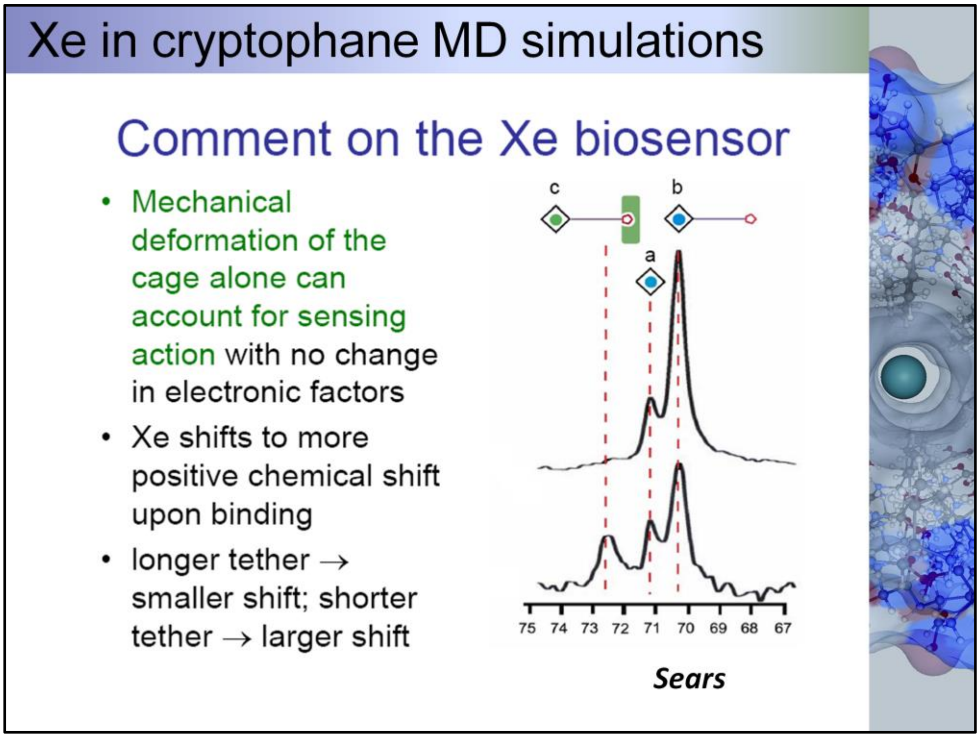
Brotin et al.
Eur. J. Org. Chem.
2003, 973-984

Our Monte Carlo SIMULATIONS

using <u>the same</u> shielding functions <u>the same</u> potential functions

Sears

By doing canonical Monte Carlo averaging of shielding for Xe in positions within the cage, using THE SAME mathematical shielding surface and THE SAME potential functions for Xe-site interactions for ALL these cages, we find that we can reproduce the relative Xe chemical shifts quite well for the series of 4 cages.



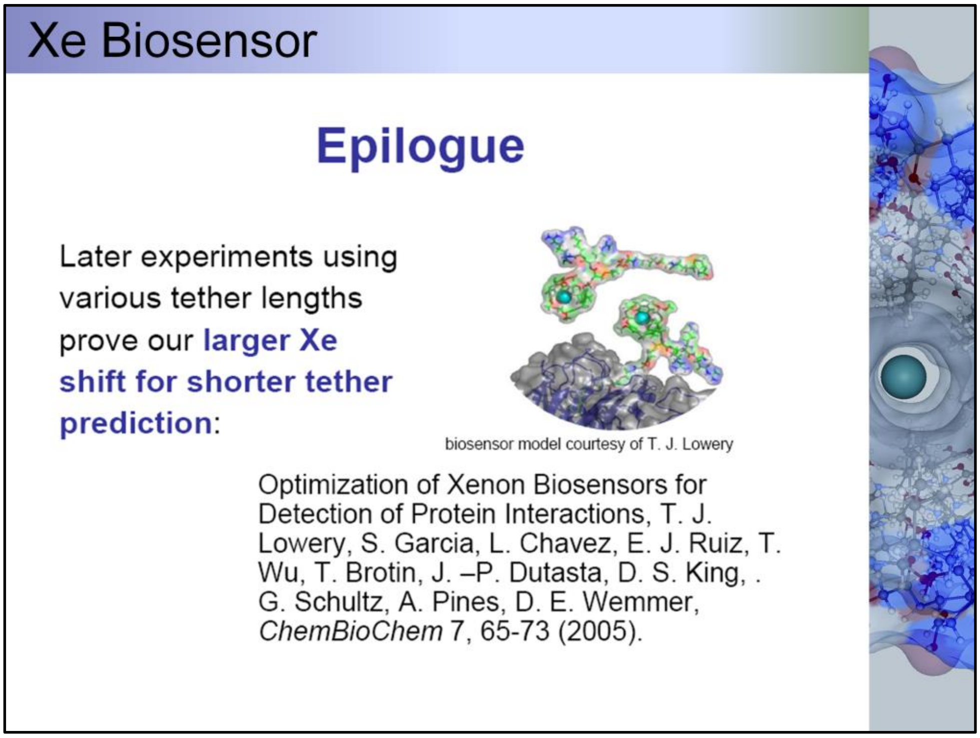
Xe in cryptophane MD simulations

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

Sears

We also carried out molecular dynamics (MD) simulations in which we permit the cage to undergo classical dynamic motions using a force field in the presence of a large protein. When we do the canonical average for Xe in the cryptophane-A cage using instantaneous (deformed) cage configurations pulled from the MD simulations, we find that we can explain the direction of the shift, that is, we have discovered the mechanism for the sensing action. Any deformation of a symmetrical quasi-spherical cage like cryptophane-A necessarily leads to a reduction in the internal volume of the cage. The closer the cage is to the large protein, the greater the deformations resulting from bumping into the protein. Therefore, we predicted in 2003: the shorter the tether, the larger will be the Xe chemical shift upon binding (relative to the free sensor in solution). In the limit of the very long tether, the Xe chemical shift upon binding goes to zero.



Xe Biosensor

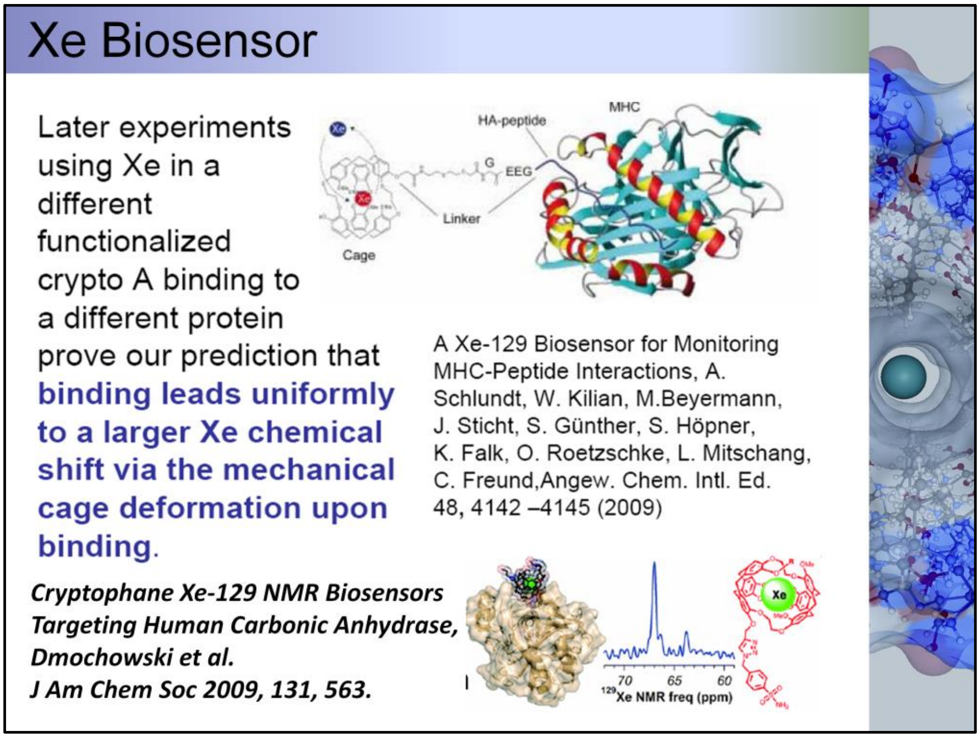
Epilogue

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).

Since the biosensor syntheses are very involved, it took several years before the experimentalists could investigate the dependence of the Xe chemical shift on the tether length. Eventually, in 2005, they found agreement with our predictions, thereby verifying the mechanism for the sensing action that we proposed.



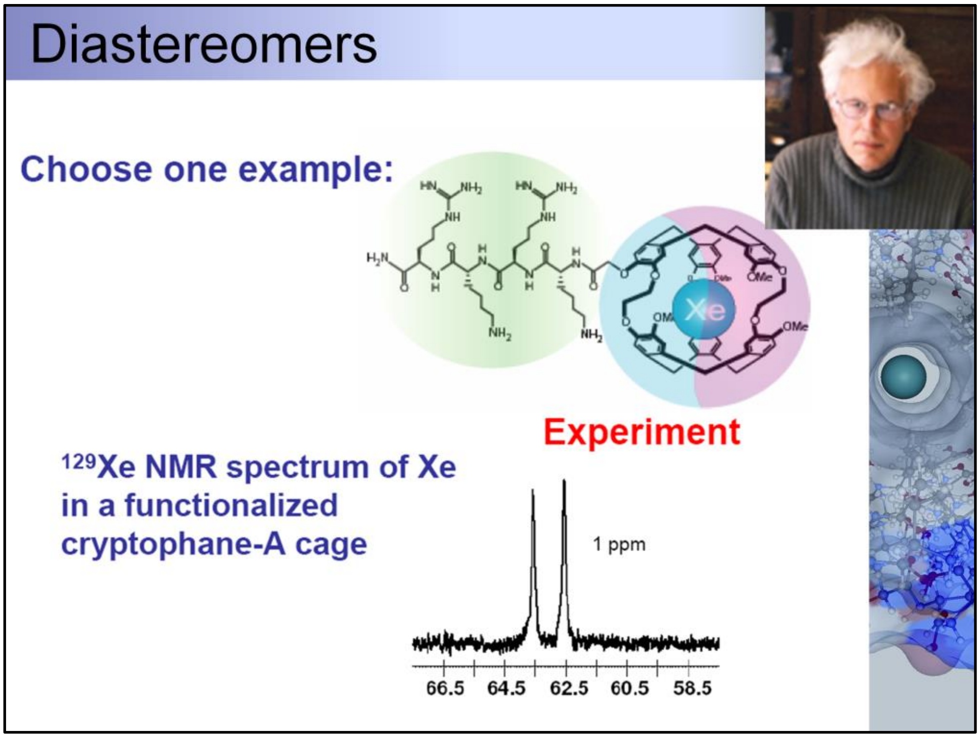
Xe Biosensor

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**.

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)

Cryptophane Xe-129 NMR Biosensors Targeting Human Carbonic Anhydrase, Dmochowski et al. J Am Chem Soc 2009, 131, 563.

Other groups have since adapted the Pines-Wemmer work and synthesized similar biosensors. Their findings in 2009 also verify our predictions.



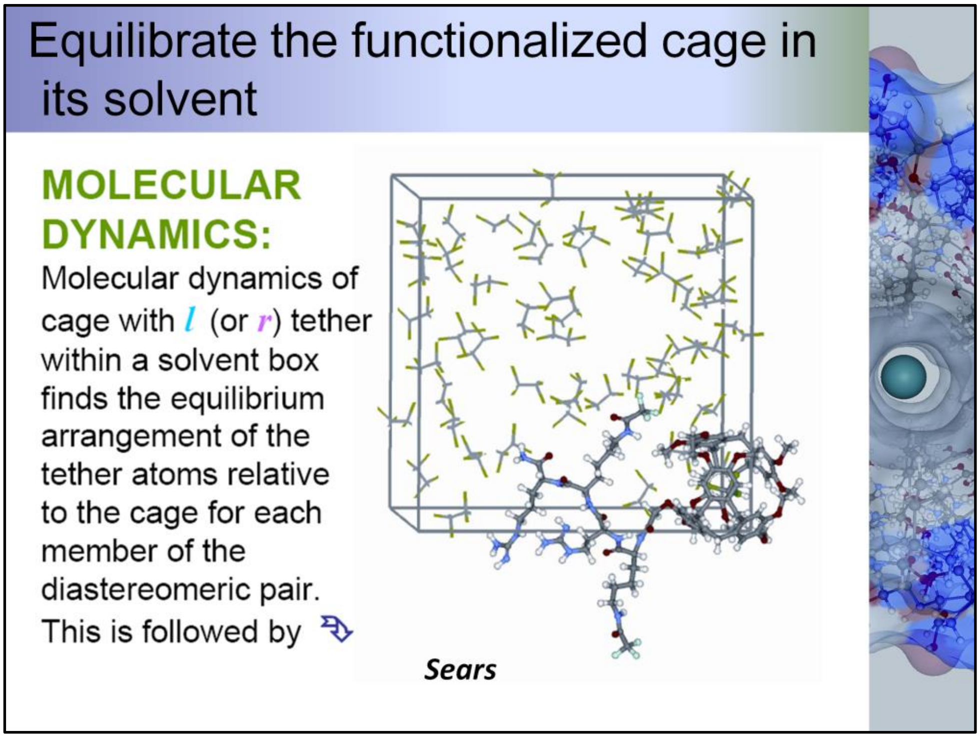
Diastereomers

Choose one example:

Experiment

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

We would not have ventured into chirality without Bob Harris, the chirality guru. We started from bare bones: an electron on a helical line, Xe in a helix of Ne atoms, and made chiral fields with helix of point charges in order to see how well can Xe shielding respond to these chiral fields. Eventually, we wanted to understand the direction and order of magnitude of the diastereomeric shifts observed by the Alex Pines group, one example is shown here. Since the cage is chiral and a racemic mixture of left- and right-handed cages are used in making the biosensor, the attachment of left-handed functional groups creates a diastereomeric pair. Signals from both are observed but the assignment of the Xe chemical shifts to LL and RL respectively is not possible without actually doing the synthesis with a cage of pure known absolute chirality. We decided to try and do the assignments theoretically. The exercises with simple Ne helices etc. were necessary to make sure that we can believe the results that we will get with the complex system, based on the deep understanding possible from the results in the simple model systems.

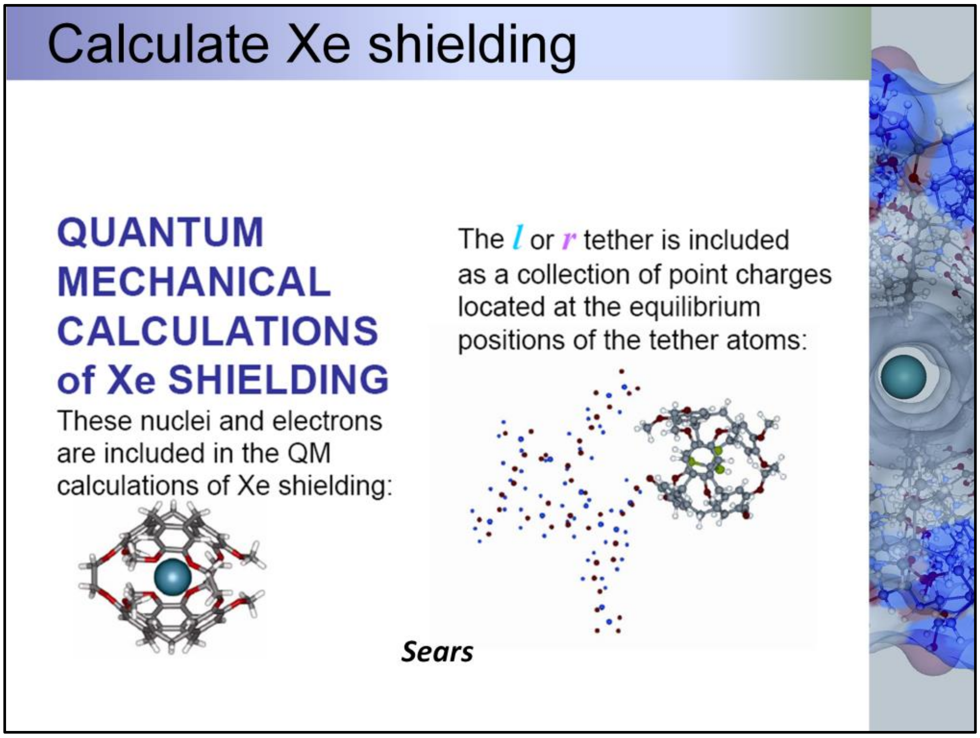


Equilibrate the functionalized cage in its solvent

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 ⇨

Sears

It is easier to use a cage of only one chirality (left-handed, say) and investigate the effects of left-handed tether versus a right-handed tether on this cage. The way in which a left-handed tether drapes itself over the left-handed cage is different from the way a right-handed tether configures itself in the immediate vicinity of the cage. Therefore, the MD simulation provides us with two different atomic configurations for the diastereomers.



Calculate Xe shielding

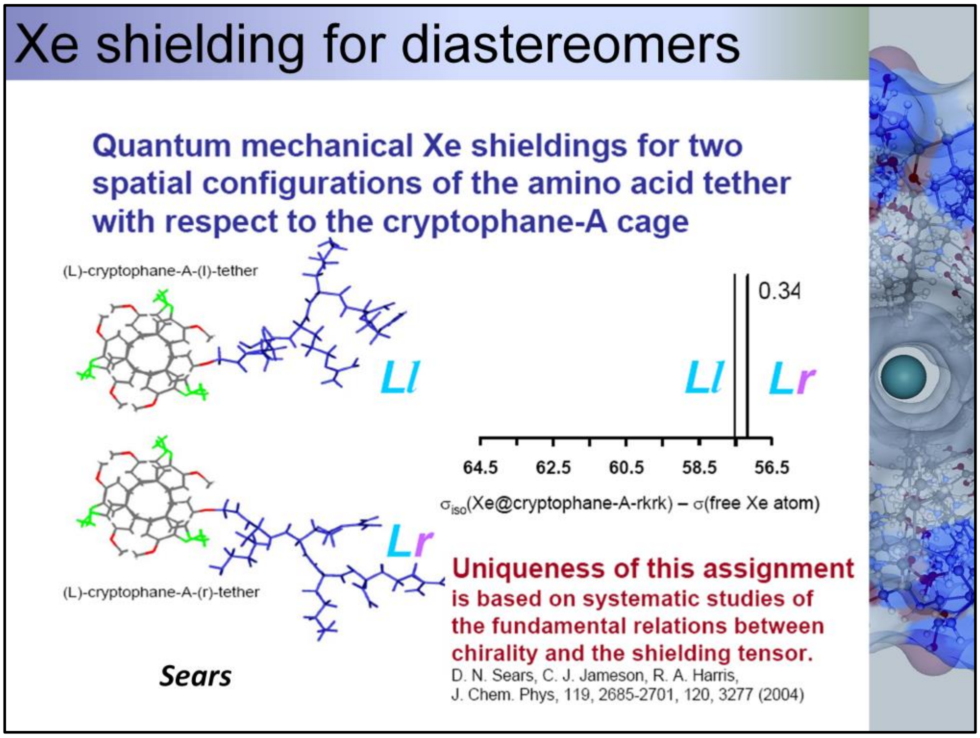
QUANTUM MECHANICAL CALCULATIONS of Xe SHIELDING

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:

Sears

The quantum mechanical calculations of Xe shielding is done in the presence of all the electrons of Xe, all the electrons of a whole cryptophane-A cage, with the equilibrium tether atomic configuration exerting its chiral field as represented by point charges.



Xe shielding for diastereomers

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

Ll

0.34

Ll Lr

64.5 62.5 60.5 58.5 56.5

σ_{iso}(Xe@cryptophane-A-rkrk) – σ(free Xe atom)

Lr

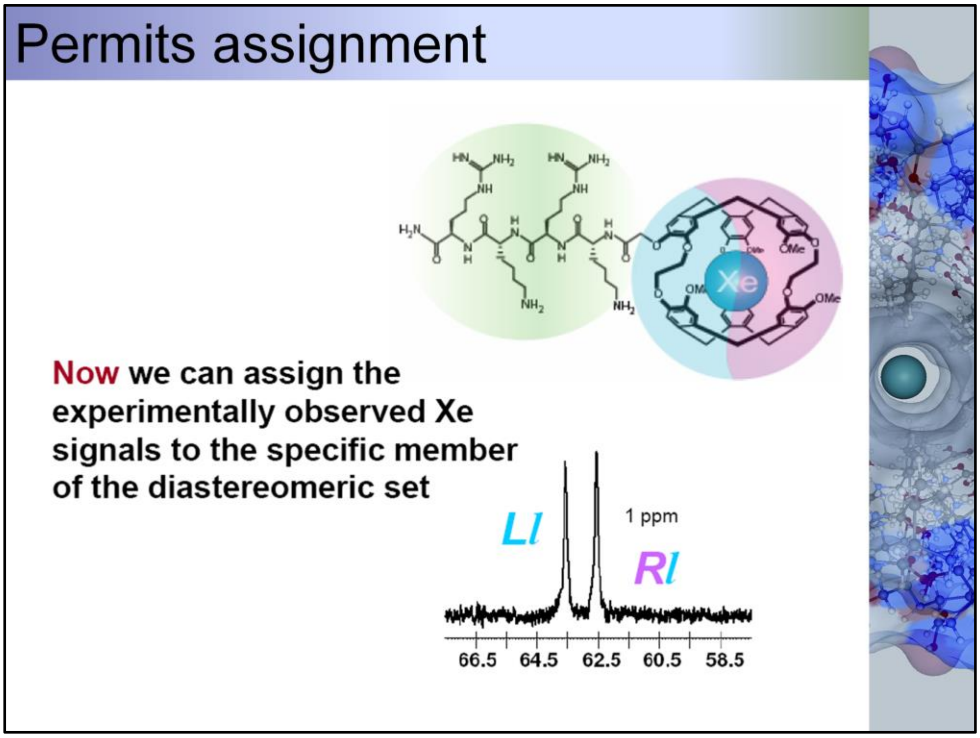
(L)-cryptophane-A-(r)-tether

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)

Sears

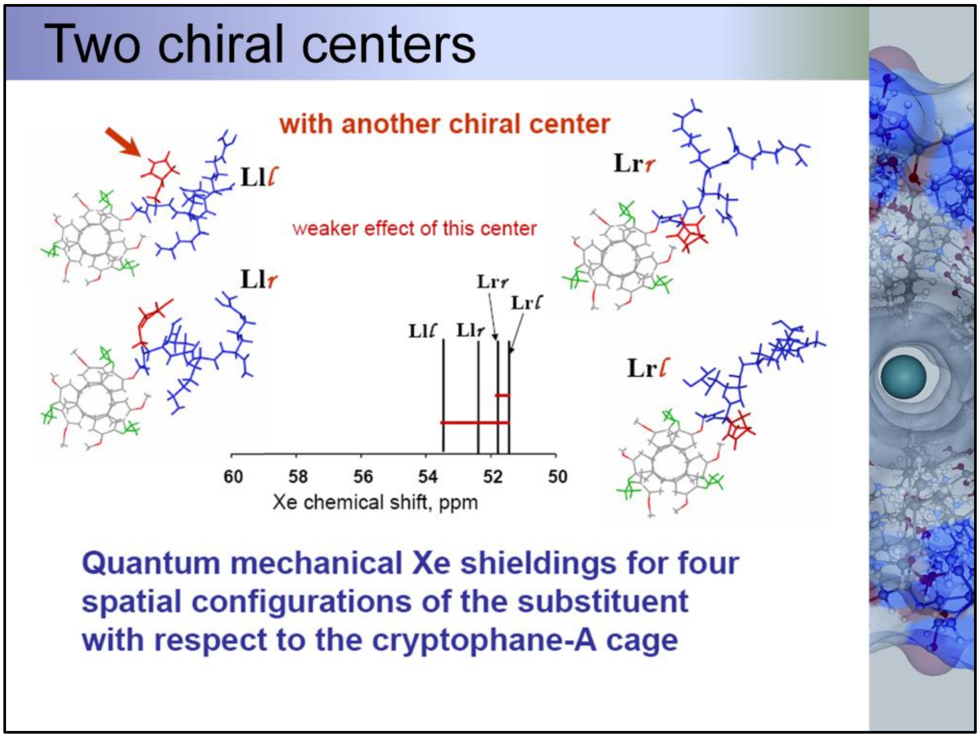
Using a single-position for Xe (a typical one inside the cage), we do the one-point calculation for the Ll and the Lr diastereomers.



Permits assignment

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

Thus, we are able to assign which member of the diastereomeric set gives which Xe chemical shift.



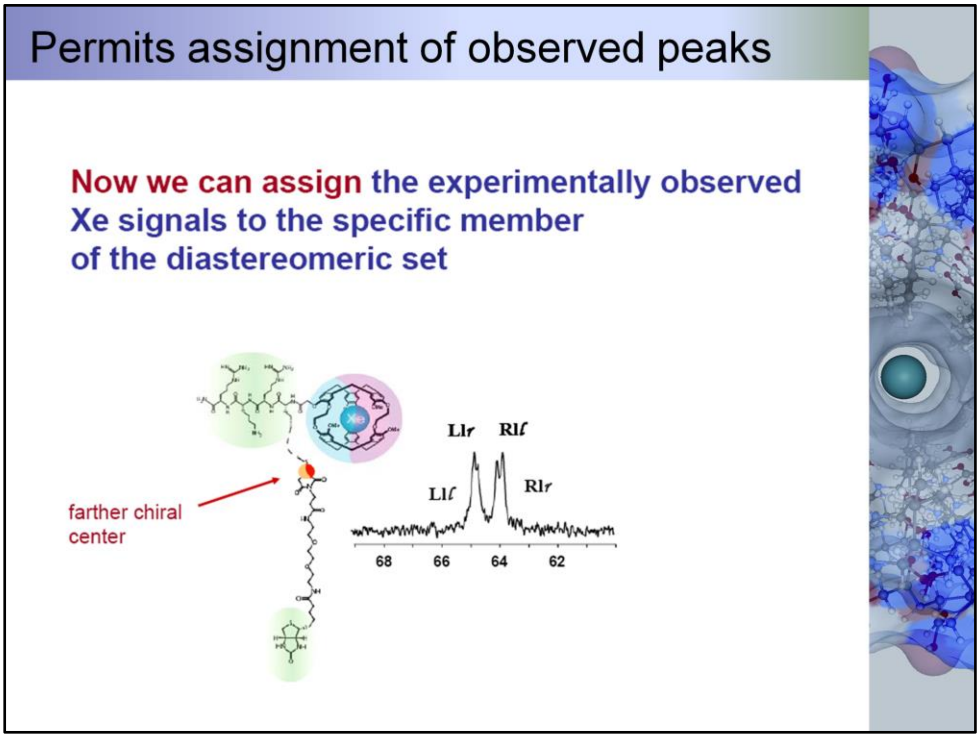
Two chiral centers

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

We have done these calculations even for the case of two chiral centers on the tether, and find that one chiral center (the one farther out from the cage) exerts a weaker chiral influence on the Xe shielding.

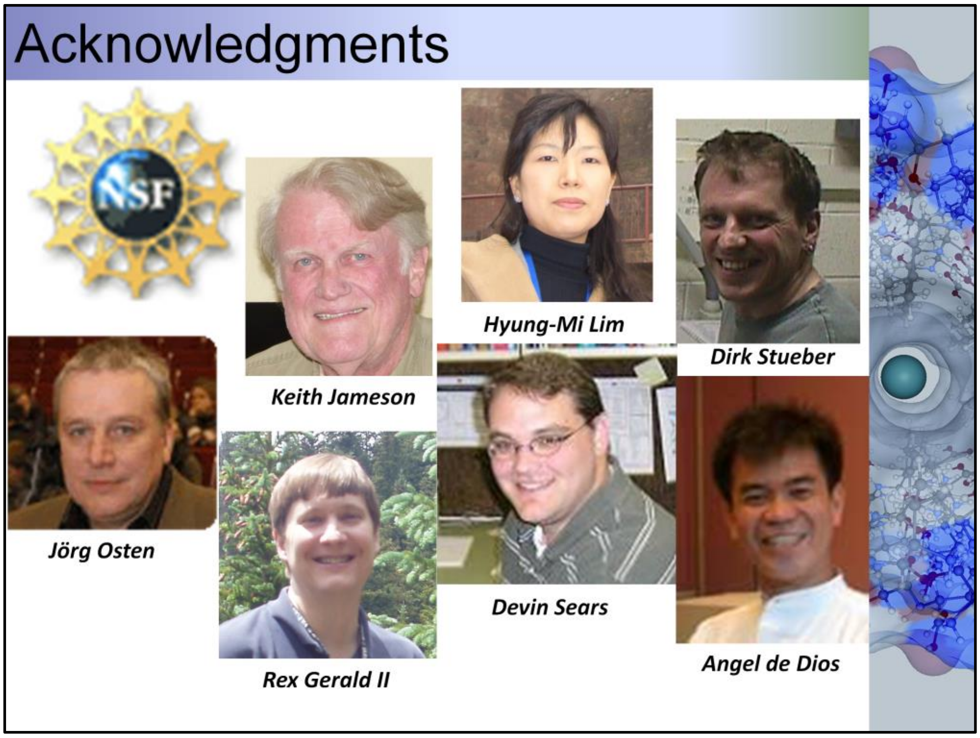


Permits assignment of observed peaks

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

farther chiral center

Finally we can assign all four observed peaks absolutely.



Acknowledgments

Keith Jameson

Hyung-Mi Lim

Dirk Stueber

Jörg Osten

Rex Gerald II

Devin Sears

Angel de Dios

Thank you for your attention. I thank NSF which has supported my research over the entire period of my career. I include here only those individuals whose work I mentioned in this talk: Keith Jameson, my partner in crime who took part in ALL of the EXPERIMENTS in my lab; Hyung-Mi Lim did the ab initio calculations of rare gas in zeolite fragments and the GCMC simulations of Xe and of Xe-Kr, Xe-Ar in NaA; Rex Gerald did the experiments and analysis of spectra of Xe in zeolite NaA; Angel de Dios did all the ab initio calculations of Ar intermolecular shielding surfaces, and intramolecular shielding surfaces, and much much more; Devin Sears did all the work on cryptophanes and everything I mentioned involving MD, diastereomers, lineshape calculations in dipeptide channels and TPP. Jörg Osten worked on isotope effects on shifts and J coupling. Dirk Stueber did the Xe in clathrate hydrates calculations.