

Xe NMR

Cynthia J. Jameson

University of Illinois at Chicago, Chicago, USA

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1 INTRODUCTION

The extremely high sensitivity of the ^{129}Xe NMR chemical shift to its environment has made the Xe atom a widely used probe in the characterization of microporous materials such as zeolites, polymers, graphite, coals, and other materials. In zeolites, the ^{129}Xe chemical shift is known empirically to depend on zeolite pore and channel dimensions, on its Al/Si ratio, cation distribution, location of cations, coadsorbed molecules, dispersed metal atoms, and paramagnetic ions, blockage of pores by coking, and domains of different composition or crystallinity. Some of these applications have been reviewed (see *Microporous Materials and Xenon-129 NMR*) and have been comprehensively reviewed by Fraissard and coworkers.¹ By transferring angular momentum from laser light to electronic and nuclear spins, optical pumping methods can increase the nuclear spin polarization of noble gases by several orders of magnitude, thereby greatly enhancing their NMR sensitivity. This methodology has been described (see *Polarization of Noble Gas Nuclei with Optically Pumped Alkali Metal Vapors*). The enormous sensitivity enhancement afforded by optical pumping can be exploited to permit a variety of novel NMR experiments across numerous disciplines. Many such experiments are reviewed by Goodson, including the void-space imaging of organisms and materials, NMR and MRI of living tissues, probing structure and dynamics of molecules in solution and on surfaces, NMR sensitivity enhancement via polarization transfer, and low-field NMR and MRI.² Further applications of hyperpolarized xenon to biology and medicine³ and to materials have been reviewed.⁴

In porous solids where the geometric confinement of the Xe does not permit isotropic averaging, the observed Xe line shape reflects the average chemical shift tensor, a tensor resulting from averaging over a distribution of heterogeneous environments. This distribution of environments depends on the morphology of the material, the nature and the connectivity of the pores, the temperature, and the Xe loading. In this article, we answer the question: what information can Xe NMR spectroscopy provide about the system? The studies in well-defined systems illustrate the nature of the information that can be gained in those cases where the validity of the information has been tested against other methods of characterization and

enlightened by computer simulations. The knowledge gained in these studies can be applied to the understanding of complex materials using the Xe atom as an in situ probe. The local dynamic averaging of the Xe chemical shift has been used to advantage in the development of a biosensor in which selective molecular recognition and targeted binding permits Xe NMR or MRI to detect the existence of very low quantities of the target.

2 WHAT INFORMATION CAN Xe NMR SPECTROSCOPY PROVIDE ABOUT THE ENVIRONMENT OF THE Xe ATOM?

Although the Xe NMR chemical shift is extremely sensitive to the environment of the Xe atom and can distinguish very subtle differences, the observed chemical shift is often the result of averaging over various environments. We consider the Xe spectral signature in a set of limiting cases where the dynamic averaging is limited to well-known environments, and make direct connections between the electronic and structural nature of the environment and the details of the observed spectral signatures. This knowledge will permit interpretation of Xe spectra in the more general case of wider averaging over multiple Xe environment types in typical experiments of Xe in porous solids where the occupancies of the pores are variable, and exchange between intercrystalline space, intracrystalline space, and bulk gas is significant.

2.1 One Xe Atom in a Cage in a Crystal

Even in a very small cage, an Xe atom averages over many positions in the NMR time scale of the span of the shielding tensor. For example, the interactions of an Xe atom with the C atoms in C_{60} have been found to be theoretically consistent with the Xe atom averaging over positions close to the center of the cage rather than an immobile Xe fixed at the center of the cage.⁵ This is the simplest case, a definite single occupancy and no Xe exchange with sites outside the cage. The Xe chemical shift for $\text{Xe}@\text{C}_{60}$ is 182.35 ppm relative to free Xe atom.⁶

Anisotropic powder patterns have been reported for Xe in a cage in clathrates and inclusion compounds where the Xe atom has sampled the environment inside one cage only. No exchange with the outside occurs in these clathrates where the cages self-assemble around the Xe atom. Depending on the symmetry of the cage, the average Xe chemical shift tensor may have one, two, or three unique components. For fast intracage averaging of an Xe atom in a cage that has symmetry lower than T , T_h , T_d , O , O_h , or K_h , the average Xe chemical shift depends on the orientation of the cavity in the external magnetic field. A sample containing randomly oriented crystals will then exhibit a powder pattern for each $\text{Xe}@\text{cage}$. The powder pattern reflects an average shielding tensor.

The Xe line shapes in clathrate hydrates Structure I, Structure II, and H have been observed by Ripmeester and coworkers,⁷ and the canonical Monte Carlo averaging of the quantum-mechanically calculated Xe shielding tensors in the various clathrate structures^{8,9} agree well with the observed average tensors in the number and relative magnitudes of

the unique tensor components in 12 different cages. The number of unique tensor components in both experiment and simulations is found to be consistent with that predicted by Buckingham and Malm¹⁰ for the point group symmetry of the nuclear site at the center of the cage. The average shielding tensors for the Xe atom inside a cage reflect the idealized cage symmetry because equivalent sampling of equivalent Xe positions, each characterized by asymmetric instantaneous shielding tensors, result in cancellation of opposite-signed off-diagonal elements, since the probabilities of finding the Xe in equivalent locations are equal, leaving only the noncanceling parts to survive.

The general nature of the Xe intermolecular shielding function (becoming more deshielded with closer approach of a neighbor atom) combined with the general nature of Xe one-body distribution functions in concave spaces leads to (i) the isotropic parts of the Xe chemical shift tensor correlating with cavity size for similarly constituted cavities, and (ii) the relative magnitudes of the average tensor components directly correlating with the symmetry and the aspect ratio of the cage dimensions. The isotropic part of the average Xe chemical shift tensors exhibit the general correlation that smaller cages give rise to larger Xe deshielding.

Thus, the studies of a single Xe atom in a cage provide the following insights: the isotropic part of the average Xe NMR chemical shift tensor correlates with the size of the cage. The Xe NMR lineshape directly provides information about the symmetry of the cage and the aspect ratio of its dimensions. This information comes from the number of unique tensor components, and the relative magnitudes of the components parallel and perpendicular to the symmetry axis of the cage itself. These types of structural information can be deduced directly from observations of Xe NMR spectra provided that the Xe in the cage is not undergoing fast exchange with other sites within the crystal or in the overhead gas (the cases considered in this section “One Xe Atom in a Cage in a Crystal”).

2.2 One Xe Atom in a Flexible Cage in Solution

For an Xe atom in the organic cage of cryptophane-A the Xe chemical shift is 63 ppm¹¹ while in the somewhat larger cage of the same type, cryptophane-E, it is 30 ppm smaller.¹² Monte Carlo averaging of the quantum-mechanically calculated Xe shielding tensors¹³ reproduced the correct sign and magnitude of the observed Xe chemical shift for Xe@cryptophane-A relative to the free Xe atom, the Xe chemical shift for Xe in the larger cryptophane-E cage, and the correct relative Xe chemical shift of about 30 ppm between these two cages. The chemical shift relative to the free Xe atom is smaller in the larger cryptophane-E cage than in the cryptophane-A cage for the same reason that, for clathrate cages, Xe chemical shifts are found to be smaller for the larger cavities. Even the small changes in the Xe chemical shifts upon successive deuteration of the cryptophane cage¹¹ can be reproduced by taking into account that the effective volume occupied dynamically by the deuterium atoms is slightly smaller than that of the hydrogen atoms because of the greater vibrational amplitude of the C–H compared to the C–D. This difference leads to a slightly larger free volume for the Xe in d_n -cryptophane-A than in h_n -cryptophane-A. The general nature of the

Xe intermolecular shielding becoming more deshielded with closer approach then provides the correct sign of the Xe chemical shift upon deuteration.

These cages are flexible; this is distinct from the clathrate hydrate cages, which are more rigid. The flexibility of the cage has significant ramifications vis-à-vis the temperature dependence of the Xe chemical shift (see the section “Variable Temperature and Fixed Xe Occupancy”). In this example, the Xe spends a finite time in residence within the cage, but has the ability to exchange with Xe atoms in the solution outside the cage. The Xe exchange events are used to advantage in the biosensor described in the section “Xe as an Integral Part of a Biosensor.”

2.3 More than One Xe Atom in a Cage in a Crystal

In some cases, the clathrate cages can be large enough to accommodate two Xe atoms. An example is Xe clathrate of Dianin’s compound,¹⁴ where hourglass-shaped cavities, which can accommodate one or two Xe atoms, stack to form columns along the c -axis of the crystal. The Xe NMR line shapes in both the singly occupied and the doubly occupied cavities are observed to be axially symmetric, with the two-Xe case exhibiting a larger isotropic shift (154 ppm vs 134 ppm) and smaller span than the one-Xe case. Double quantum NMR permitted definitive assignments of the peaks. X-ray diffraction confirms that Xe atoms are located at the widest portions of the hourglass-shaped cavity, but is unable to distinguish between double occupancy of a cavity and disorder over symmetry-related sites in singly occupied cavities. However, Xe NMR can easily distinguish between cavities single and double-occupied because of the sensitivity of the Xe chemical shift to the local environment. The component of the shielding tensor along the hourglass axis is the same for both cases since this component arises entirely from the interactions between Xe and the wall atoms circling it in the widest portion of the cavity. Because shielding operators involve the angular momentum operators, the only electron densities that can contribute significantly to the shielding tensor component along a particular axis are those that are in the plane (containing the NMR nucleus) perpendicular to the axis. This is highly deshielding because there are several atoms and they are close to the Xe. On the other hand, the tensor components in the plane perpendicular to the hourglass axis are different for both cases. These perpendicular components arise from interactions between Xe₁ and the atoms of the hourglass cavity lying on a plane along the long direction of the hourglass. This is not as deshielding as the component along the cavity axis because at most only two wall atoms are close and the others are much farther away. For the Xe tensor in the doubly occupied cavity, there is the additional contribution coming from interaction with the second Xe, which, on the average, is 4.7 Å away. This results in a greater deshielding for the perpendicular component for the doubly occupied cavity. Thus, we can understand how every aspect of the structure of the cavity contributes to the shielding tensor components in the doubly occupied as well as the singly occupied cavity. There is a direct connection between these aspects of the structure and the observed average chemical shift tensor components. The concept of the quantum-mechanically determined greater *deshielding* accompanying closer approach of the other atom

to Xe is an intrinsic part of the understanding of the averaging of Xe chemical shift tensors for Xe inside pores.

The alpha cages of crystalline zeolite NaA can accommodate 1–8 Xe atoms, and the residence times are sufficiently long to permit observation of independent occupancies Xe_1 , Xe_2 , Xe_3 , ..., Xe_8 ,¹⁵ so that the distribution of occupancies at any overall Xe loading can be measured from the NMR spectrum, and the average Xe chemical shift in each n -occupied cage can be separately followed as a function of temperature. These chemical shifts did not appear to depend on the overall Xe loading. The distributions and Xe_n chemical shifts could be reproduced by grand canonical Monte Carlo simulations.¹⁶ The cages are nearly symmetric and the lineshapes appear relatively isotropic. The chemical shifts and Xe atom distributions are found to depend on the counterions (K^+ vs Na^+). For the $Xe_1@$ cage, the same connection between the aspects of the cage structure and the isotropic part of the chemical shift tensor can be made, as in the section “One Xe Atom in a Cage in a Crystal.” The characteristics of the cage (including the types of counterions) determine the chemical shift. What is new here is that the Xe has a finite residence time within the cage and the fraction of such singly occupied cages depends on the temperature and overhead Xe gas pressure, with the adsorption isotherm of Xe in the zeolite determining the fractions.

The various $Xe_n@$ cage exhibit systematically larger chemical shifts with increasing n for the same reasons that the chemical shift of the $Xe_2@$ Dianin’s compound clathrate is greater than that of $Xe_1@$ Dianin’s compound clathrate. The other $n-1$ Xe atoms at close proximity provide additional deshielding contributions. If this were all that is needed to be considered, then the incremental chemical shifts with increasing n should be equal. This should not be the case because the free volume available to the Xe atom is increasingly smaller with greater number of coinhabitants of the cage, leading to systematically shorter Xe–Xe distances over which the averaging can take place in an increasingly crowded cage. It is this latter aspect of the averaging and the nature of the Xe intermolecular shielding function becoming increasingly deshielded with shorter distances that makes the incremental chemical shift with increasing n become more pronounced. This is particularly severe when the cage is more than half filled. The large chemical shift differences among the various $Xe_n@$ cage signals permit the following experiments: (i) the temperature dependence of the Xe_n chemical shift could be obtained for each; (ii) the cage-to-cage migration of Xe atoms could be determined by 1-D-EXSY or 2-D-EXSY, with the former providing more precise and more accurate rate constants for the Xe leaving from a cage containing n atoms to go into an adjacent cage containing $(p-1)$ atoms, for p , $n = 1-8$ ^{17,18}; and (iii) in competitive adsorption of Xe and another gas A ($A = Ar, CH_4, CO, N_2, CO_2$, for example), the Xe chemical shift of the peaks corresponding to $(nXe+(m)A)@$ cage permits the determination of the average number of A atoms, $\langle m \rangle$, occupying the same cage as n Xe atoms for a particular overhead gas mixture (total pressure and mole fractions of Xe and A). Thus, Xe NMR gives very detailed information about competitive adsorption (see, for example, studies of competitive adsorption of Xe and Ar,¹⁹ and of Xe and CH_4 in zeolite NaA²⁰).

2.4 One Xe Atom in Interconnected Cages or Channels in a Crystal

One Xe atom averaging its chemical shift by fast diffusion through interconnected cages or channels can be observed by doing Xe NMR at extremely low Xe loading conditions in the sample. Nearly all the Xe atoms are inside, so the chemical shift of the observed peak is that characteristic of the “inside” average chemical shift, hardly contaminated with the bulk gas contributions to the average in this fast-exchange system. The use of hyperpolarized Xe (see *Polarization of Noble Gas Nuclei with Optically Pumped Alkali Metal Vapors*) makes this measurement possible in a single-transient experiment. For example, the observations in zeolite SSZ-24²¹ and in a single crystal of silicalite²² using hyperpolarized Xe in a continuous-flow experiment under very low mole fractions of Xe in the flowing gas permitted the determination of the average Xe chemical shift tensors, both of which could be semiquantitatively reproduced by grand canonical Monte Carlo simulations.²³ The relative order of the Xe tensor components observed in the nearly empty crystal is a property of the channel architecture.²⁴ The nearly circular cross section of the channels in zeolite SSZ-24 makes it possible to predict the number of unique tensor components and the sign of the anisotropy, even without benefit of simulations. Predictions of Xe average shielding tensors in various types of cages and channels can be made²⁴ using the understanding of the nature of the Xe intermolecular shielding function (which becomes increasingly deshielded at closer distances) and the component of the shielding tensor along a particular axis, which comes from contributions from atoms having electron densities on the plane containing the NMR nucleus and perpendicular to that axis (derived from the shielding operators involving the electronic angular momentum operators).

The simulations in SSZ-24 provide $\delta_{zz}-\delta_{xx} = 20$ ppm, with the zz component along the axis of the channel (c -axis of the crystal),²³ whereas the experimental anisotropy is about 25 ppm. The simulations of the Xe spectra in single-crystal silicalite permitted the assignment of the tensor components along the crystal axes.²³ This anisotropy of the tensor could not be observed for Xe adsorbed in fine powder silicalite samples because under fast exchange the Xe can average not only within one crystal at a particular orientation in the magnetic field but over many crystallites in different orientations with respect to the magnetic field.

2.5 Variable Xe Occupancy in Interconnected Cages or Channels in a Crystal

Although using the hyperpolarized Xe at very low Xe mole fraction in the continuous-flow experiment can provide useful information in many cases (see the section “One Xe Atom in Interconnected Cages or Channels in a Crystal”), definitive information about the structure of the interconnected pores can sometimes be obtained only by a systematic study of Xe spectra as a function of Xe occupancy. This entails measuring the adsorption isotherm and working with thermally polarized Xe in pressurized samples.

The systematic change in the anisotropy of the average Xe tensor from one sign to another with increasing occupancy, for example, $\delta_{\parallel} > \delta_{\perp}$ at near-zero occupancy going to $\delta_{\perp} > \delta_{\parallel}$

at full occupancy, is an Xe NMR signature of a nanochannel with a cross section having an aspect ratio very close to 1.²⁴ In a typical narrow-bore channel, with dimensions such that Xe atoms can not pass each other in the channels, the tensor component whose average remains essentially constant from zero to full occupancy is the component that is along the axis of the channel, since this component comes from the circle of atoms around the Xe position in the plane perpendicular to the axis of the channel.²⁴ In Monte Carlo simulations in such systems, there are no contributions from Xe–Xe dimers whose centers lie in a plane perpendicular to the channel axis. Thus, the tensor component along the channel axis consists only of averages over Xe–wall contributions.

Averaging in static channels (assumption of rigid zeolite crystalline structure) results in only a slight increase in the Xe–wall contributions to this tensor component with increasing Xe occupancy, and the component which does not change with occupancy can be assigned to the channel axis direction, with confidence. When two of the tensor components are very close in value, a definitive assignment of a structural environment described by three unique components rather than two requires the systematic study as a function Xe occupancy, as was the case for Xe in ALPO-11.²⁵ The systematic linear change of each of the three unique tensor components with Xe occupancy is a clear signature that two Xe atoms do not have electron densities on the same plane perpendicular to the channel axis. In this particular case, this is ensured by the structure of the channel walls, creating a “sweet spot” for interactions with the Xe at periodic positions along the channel, with high probabilities of finding the Xe, yet permit the Xe to be at short distances when all such sweet spots are occupied.

Monte Carlo averaging of the Xe chemical shift tensor in model channels of elliptical cross section has revealed the following:²⁶

1. The average Xe chemical shift tensor under conditions of nearly zero occupancy is a signature of the channel architecture. The number of distinct components and the relative order of the principal tensor components (i.e., the assignments of the components to the crystal axes) for any elliptical nanochannel at near-zero occupancy is $\langle\delta\rangle_{bb} < \langle\delta\rangle_{aa} < \langle\delta\rangle_{cc}$, where c is the channel axis direction, and a is the longer axis of the elliptical cross section. In other words, the tensor components from the spectrum are easily unequivocally assignable with respect to the crystal axis directions.
2. The Xe-channel contributions to the average chemical shift tensor are nearly independent of the Xe occupancy.
3. The Xe–Xe contributions to the average chemical shift tensor have a relative order of components that are exactly opposite to that of the Xe-channel contribution, i.e., $\langle\delta\rangle_{cc} < \langle\delta\rangle_{aa} < \langle\delta\rangle_{bb}$.
4. This relative order of the Xe–Xe contributions to the tensor is maintained for any Xe occupancy from nearly zero up to full, provided the channel cross section is small enough that Xe atoms cannot pass each other in the channel, in which case, the Xe–Xe contributions to the component along the channel axis $\langle\delta\rangle_{cc}$ is also very different from the other two components, in that it is small (shielding is nearly unchanged from the free Xe atom), and changes very little, and is in the same direction as the other two components.

5. The effective size of the atoms constituting the nanochannel influences the Xe–Xe contribution to the tensor. Larger more polarizable atoms lead to larger magnitudes of the Xe–Xe chemical shift tensor components.
6. The effective polarizability of the constituent atoms determine the magnitude of the Xe shielding response and therefore determine the magnitudes of the individual tensor components that will be observed at nearly zero occupancy.
7. The total average chemical shift tensor that is observed, being a sum of Xe-channel and Xe–Xe contributions, reflects the channel architecture in the number of unique components, and the number is unaffected by the atomic constitution of the channel.
8. That component of the average chemical shift tensor parallel to the channel axis remains nearly invariant with occupancy number (provided the channel cross section is small enough that Xe atoms cannot pass each other in the channel).
9. The relative order of the tensor components (i.e., the assignments of the components to the crystalline axes) does change with occupancy, a consequence of the fact that the magnitudes of the individual tensor components change with occupancy in a systematic way that is nearly independent of the nature of the atoms constituting the channel.
10. The two components of the total chemical shift tensor perpendicular to the channel axis remain in the same relative order with each other, both increasing with increasing Xe occupancy in the channel, one component (the one along the short axis of the elliptical cross section, $\langle\delta_{bb}\rangle$) increasing at a slightly faster rate than the other, so that the two components, changing with occupancy in a nearly parallel fashion, nevertheless, tend slightly toward each other with increasing occupancy.

When the interconnected cavities or channel permits Xe to be close to each other at high occupancies, the systematic increase of the chemical shift component perpendicular to the channel axis can be expected and is observed. This is a consequence of the intermolecular shielding function becoming sharply more deshielded with shorter distances. The increase in the perpendicular components can be sufficiently pronounced that as it crosses past the nearly unchanging parallel tensor component, a change in the sign of the axiality of the tensor occurs in going from nearly empty to fully occupied. This has been observed for Xe in tris(*o*-phenylenedioxy) cyclophosphazene (TPP).²⁷ On the other hand, when this systematic increase of the chemical shift component perpendicular to the channel axis is relatively small, even upon increasing overhead Xe pressures, then this is a clear indication that the interconnected cavities or channel has a structure that constrains the Xe atoms at average positions sufficiently removed from each other in the fully occupied channel, such as when there are constrictions along the channel, which keep the Xe within structure-defined cavities along the channel. The latter was found to be the case for Xe in the channels of $(\pm)\text{-[Co(en)}_3\text{]Cl}_3$, where only modest increases of the perpendicular components are observed with increasing Xe occupancy and no crossing over of components is observed, even at high overhead pressures.²⁸

2.6 One Xe Atom in a Flexible Channel

Self-assembling structures with nanochannels such as TPP (see the section “Variable Xe Occupancy in Interconnected Cages or Channels in a Crystal”), which forms a fairly rigid molecular crystal, have been probed with Xe. Other examples are peptide nanochannels formed through aggregation of dipeptides in a head-to-tail hydrogen-bonded network, forming a channel with a hydrophobic interior. Two such systems, the dipeptide L-Val-L-Ala and its retroanalogue L-Ala-L-Val (hereinafter VA and AV, respectively) have been used to characterize the Xe chemical shift tensors in hydrophobic channels,²⁹ which would serve as models for Xe in hydrophobic pockets in folded proteins. In these two channels, the Xe chemical shift tensor as a function of occupancy has been observed and reproduced with grand canonical Monte Carlo averaging of quantum-mechanically calculated Xe shielding functions. The variation of these line shapes with occupancy is found to be typical of narrow-bore channels, which could have been predicted without benefit of simulations. Here, the side chains of the peptides are $-\text{CH}_3$ groups, so the entire channel provides CH_3 -lined channel walls. The adsorption isotherm could be closely reproduced by the simulations, despite the assumption of Xe- CH_4 potential functions for the Xe- CH_3 interactions within the channel. The channels in these dipeptides are flexible.

Xe in other dipeptide molecular crystals were studied, with CH_3 -lined channel walls arising from side chains such as CH_3 , isopropyl, sec-butyl, isobutyl, and hydroxyl methyl.³⁰ In addition to Ala-Val (AV), Val-Ala (VA), Xe adsorption in dipeptides Leu-Ser (LS), Ala-Ile (AI), Val-Val (VV), Ile-Ala (IA), Ile-Val (IV), Val-Ile (VI) (all LL isomers) was monitored in situ with continuous-flow ^{129}Xe NMR spectroscopy over a temperature range of 173–343 K. The interpretation of the line shapes and chemical shift anisotropy as a function of temperature provided information on the structure of the xenon-cavity complex, the interpretation made possible by taking into account the helicity and flexibility of the nanochannels and the dynamics of xenon. The principal tools used in the interpretation are the same as the ones that we have been using in the simpler systems already described up to this point: the general behavior of the Xe intermolecular shielding function with decreasing distance, the nature of the shielding tensor components being dictated by the involvement of electronic angular momentum operators in the shielding operators, and the thermodynamic behavior dictated by potential functions consisting of pairwise interactions together with the structural arrangement and the electronic nature of the atoms that constitute the channel walls. The potentials determine the probable distribution of the Xe in the channels, leading to adsorption isotherms, one-body and two-body distribution functions, and the Xe and molecular crystal dynamics as a function of temperature. The averaging of the components of the shielding tensor is dictated by these dynamics and distributions weighting the shielding tensor components appropriate for particular instantaneous atomic arrangements. Adopting these principal tools, and making the Xe NMR measurements, provides an approach that is a powerful way of analyzing pore space in soft microporous materials, yielding a quantitative thermodynamic description of sorption and the characteristics of the pore space and sorption events that occur on molecular-scale level during pore filling.³⁰

One particularly interesting aspect of flexible channels is that unlike zeolites or other inorganic materials, the pores do not maintain their shape and cross section for all sorption levels. The deformation of the porous framework upon adsorption of Xe, their structural “softness”, and the capability of easy structural transformations distinguish them from inorganic channels. The interaction between Xe and hydrophobic channels can be significantly strong to permit Xe to enter and fill flexible channels whose X-ray diffraction structures correspond to channel diameters smaller than the van der Waals diameter of Xe, as in the case of Ile-Val (IV) (3.4 Å) and Val-Ile (VI) (3.0 Å).

2.7 Variable Temperature and Fixed Xe Occupancy

Understanding of the temperature dependence of the average Xe chemical shift tensors in pores comes from a combination of the same principles already applied; the nature of the shielding function with distance is convoluted with the variation of the probabilities of Xe positions with changes in temperature. The temperature dependence of the Xe chemical shift of a single Xe in a cage arises because the one-body distribution function of the Xe atom becomes less sharply peaked at higher temperatures, where the more favorable Boltzmann factor affords a higher probability of finding the Xe closer to the cage atoms. At close approach, the deshielding of the Xe is more pronounced for each type of cage atom. When the cage is small enough such that the lowest potential energy for Xe is at the center, then the potential energy for Xe becomes less attractive as Xe moves away from the center of the cage. In this case, increasing the temperature leads to increased sampling of the less attractive regions in the cage closer to the wall atoms, which distances, in turn, correspond to greater deshielding. Thus, for small cages, the Xe becomes more deshielded with increasing temperature. An example of this is Xe in cryptophane-A, which exhibits this direction of temperature dependence expected for a single Xe in a small cavity: the chemical shift increases with increasing temperature. Monte Carlo simulations of Xe in a static cryptophane-A cage reproduced the sign of the observed temperature coefficient¹³; the magnitude of the temperature dependence can only be accurately calculated by using a dynamic, flexible cage.

On the other hand, in a larger cage the center is less attractive for Xe than positions where the Xe is around 4 Å from the wall atoms. In such cages, there is a three-dimensional low-energy trough 4 Å from the wall where the Xe prefers to be. At low temperatures, the Xe would exhibit average chemical shifts that reflect the high weighting at the trough positions. As the temperature is increased, the Xe has increasing probability of being found farther away from the trough and closer to the center of the cage. These positions are farther away from the walls (less deshielded) and their increasing weight with increasing temperature leads to a decrease in Xe deshielding. Thus, a single Xe in this cage would exhibit a chemical shift that is decreasing with temperature. An example of this behavior is observed in the Xe_1 @cage in zeolite NaA,¹⁵ and this temperature dependence has been reproduced by grand canonical Monte Carlo simulations.¹⁶ When the temperature is increased further, the Xe can explore also those repulsive positions closer to

the wall atoms, and the Xe chemical shift will increase with increasing temperature, thus exhibiting a change in sign of the temperature coefficient.

When the cage is occupied by two or more Xe atoms, then there are deshielding contributions coming from the Xe–Xe interactions as well. At low temperatures, the attractive interaction between the Xe atoms would tend to keep the Xe–Xe distances close to that found at the bottom of the Xe–Xe pair potential function. Molecular dynamics simulations of 2–4 Xe atoms in a zeolite NaA cage show that the Xe atoms move around more or less in Xe–Xe pairs about 4 Å apart, like dancing partners moving apart and coming together, most of the time in pairs, ~4 Å above the inside surface of the cage. In these molecular dynamics simulations, the Xe atoms do not cross the cage from one side to the other as atoms would in a much bigger container, except at very high temperatures. At higher temperatures, the Xe also have higher probability of being found in less energetically favorable arrangements such as closer and higher up on the Xe–wall atom potential. These closer Xe–wall contributions are generally more deshielding. The Xe–Xe contributions would be either less deshielding (farther away) or when the temperature is high enough, more deshielding (closer and higher up on the repulsive wall of the Xe–Xe potential). With increasing number of Xe atoms in the cage, the Xe–Xe interactions dominate and the Xe atom loses the possibility of moving farther away from other Xe atoms. Thus, the only contributions that can operate are towards more deshielding at higher temperatures (closer and higher up on the repulsive wall of the Xe–Xe potential). This interplay between the contributions as the occupancy goes up leads to temperature dependencies for the Xe_n which change in slope, with increasing temperature, a decreasing chemical shift for the Xe_1 @cage, and changing toward a sharply increasing chemical shift for the Xe_8 @cage. This is indeed what is observed experimentally and reproduced by grand canonical Monte Carlo averaging.^{15,16}

Just as the temperature dependence of the fully occupied cage Xe_8 is dominated by the Xe–Xe contributions, the temperature dependence of fully occupied channels is too. The Xe–Xe contributions to the tensor are also a signature of the structure of the channel since the Xe positions are constrained by the shape of the inside walls. If the channel is large enough, the Xe–Xe average distances can increase with increasing temperature as the Xe probability distribution spreads out, leading to lower chemical shifts. On the other hand, if the channel has a small cross section, there is no space for the Xe atoms to move away from each other, and increasing temperature only permits sampling of the repulsive regions of the Xe–Xe intermolecular potential regions corresponding to higher chemical shifts. An example of the former case is Xe in silicalite at full occupancy (16 Xe atoms per unit cell), where the temperature dependence of the individual shielding tensor components has been observed.^{22,31} At 300 K and also at 150 K, the order of the tensor components is $\delta_{zz} > \delta_{xx} > \delta_{yy}$ (assignments are based on the single-crystal experiments and the simulations thereof). The larger tensor components greatly increase in magnitude as temperature decreases from 300 K to 150 K, and the smallest component changes the least. The span $\delta_{zz}-\delta_{yy}$ is 24.4 ppm at 300 K, increasing to 40 ppm at 150 K. Simulations yield spans 26.8 ppm and 41.2 ppm, respectively. The large changes in the tensor components δ_{zz}

and δ_{xx} with decreasing temperature can be attributed primarily to the Xe–Xe contributions to the tensor.

2.8 Variable Temperature and Variable Xe Occupancy

In those cases where the Xe occupancy varies with temperature, there are still the temperature effects on the distribution of distances of the Xe atom from the wall and from other Xe atoms observed in the systems described in the section “Variable Temperature and Fixed Xe Occupancy.” In addition, there are the larger effects of temperature on the occupancies determined by the adsorption isotherm.

At each temperature, the chemical shift tensor observed will be that corresponding to the occupancy at that temperature; the changes associated with changing Xe occupancy are discussed in the section “Variable Xe Occupancy in Interconnected Cages or Channels in a Crystal.” As the Xe occupancy increases with decreasing temperature, the chemical shift tensor component perpendicular to the axis of the channel is expected to increase with the increasing Xe–Xe contributions. This is indeed observed for Xe in the channels of the molecular crystal of all eight dipeptides studied³⁰ as well for Xe in the channels of TPP.³²

On the other hand, since the chemical shift tensor component parallel to the channel axis is not expected to change with Xe occupancy for narrow-bore channels,²⁴ (see the section “Variable Xe Occupancy in Interconnected Cages or Channels in a Crystal”) it is expected that this component will remain unchanged as the Xe occupancy of small channels increases with decreasing temperature. This is the signature of a narrow-bore channel and has been observed for Xe in the channels of the molecular crystal of dipeptide L-Ala-L-Ile (AI) as a function of temperature, and the same trend is found for Xe in the other dipeptides studied.³⁰

3 FACTORS AFFECTING THE TYPICAL Xe NMR IN POROUS SOLIDS

In the limiting cases of the section “What Information Can Xe NMR Spectroscopy Provide about the Environment of the Xe Atom?” the crystals are sufficiently large so that the only regions for the Xe atom are the bulk gas and inside the crystal. For fine powder solids, this is no longer the case. Diffusion rates of Xe in the various regions of the sample (intracrystalline, intercrystalline, bulk gas) determine the nature of the averaging of the Xe electronic environments to yield the observed spectrum in the general case. In the most common type of measurement in which Xe reports not only on its sampling of the inside environment of a single crystal but of many crystallites, as well as the gas in the intercrystalline region, the effects of exchange between bulk gas, intercrystalline, and occluded environments determines the Xe NMR spectrum and our ability to infer the nature of the porous materials from this spectrum. At a given loading, the chemical shift average will depend on the temperature, since, as already established in the section “Variable Temperature and Variable Xe Occupancy,” the chemical shift average associated with each occupation number n and also the distribution of cavity occupation numbers within the crystallite vary with temperature. At a given temperature, the chemical shift

average will depend on the loading, since the distribution of cavity occupation numbers depends on the overall average occupancy.

Proper use of the Xe chemical shift as a probe of environment requires understanding of the dynamics of Xe among the regions in the general sample, where the chemical shift reported by Xe atom includes sampling of environments in several crystallites and in the gas in the intercrystalline region. To make the connection between the ^{129}Xe chemical shift in a sample and the geometric and electronic structure of the porous material, it is important to know the various populations of Xe atoms that contribute to the observed peak. In the NMR time scale associated with differences in Xe chemical shifts in various regions as the relevant timescale, we may consider Xe populations distributed in the sample space as follows: Reservoir I includes the Xe atoms that are in the overhead gas, far away from the crystallites and incapable of exchanging with the “inside” Xe. Reservoir IV includes the Xe deep inside the crystallites that are incapable of exchanging with the Xe atoms outside. Reservoir III includes the Xe atoms inside the crystallites that are within an exchangeable layer near the outside. Reservoir II includes the Xe atoms found between the crystallites, some of which may be adsorbed on the outside surface of the crystallite, and capable of exchanging with the Xe atoms in Reservoir III. The relative volumes of these reservoirs depend on morphology and size of crystallites, crystallite packing, and overhead Xe gas pressure. In the limiting case of very fine powder filling up that part of the sample tube within the receiver coil, there are effectively only Reservoirs II and III. In the limit of very large crystals there are effectively only Reservoirs I and IV, as in the examples in the section “Variable Temperature and Variable Xe Occupancy.” In the case of Xe in clathrate hydrates, there is only reservoir IV since the Xe atom is unable to leave the intact cage.

When the morphology of the sample is very fine crystals clumped together, with mesopores between microcrystallites, a significant fraction of Xe is adsorbed in the intercrystalline reservoirs (Reservoir II). For example, the number of Xe atoms adsorbed on the outside surfaces of silicalite microcrystallites has been found to be up to as much as six Xe atoms per unit cell beyond the full occupancy of the large crystals of silicalite.³¹ At a lower temperature, any excess Xe forms solid bulk Xe on the outside of the crystallites, clearly distinguished by its signature chemical shift, 304 ppm at 144 K, for example. However, the Xe in the mesopores between crystallites would not freeze at the same temperature as the bulk xenon on the outside of the aggregates, and would appear to be “inside” the channels of individual crystals.

When the crystals are large, the fraction of Xe atoms that are within diffusive distance of the outside surface (i.e., in Reservoir III) is small, so the true chemical shift average of the occluded (Reservoir IV) Xe atoms is observed, as in the examples in the section “Variable Temperature and Variable Xe Occupancy.” On the other hand, in a fine powder sample, a somewhat smaller apparent chemical shift partially averaged with the gas phase is observed, and the chemical shift of occluded Xe is not directly measurable from the spectrum. The fraction of Xe atoms which are adsorbed on the outside surface of large crystals is much smaller too, so that the intercrystalline (Reservoir II) Xe signal is sharp and includes fast exchange with the overhead gas (Reservoir I). In large crystals, the

Reservoir IV Xe atoms exhibit a powder pattern, which is not washed out by averaging between crystallites at various orientations. The same limiting value of the isotropic chemical shift for Reservoir IV is reached in the microcrystallites as in large crystals, except that the limiting value may not be read directly from the spectrum.

For a fine powder sample the typical observations would be as follows: in the very low loading samples, the exchange is very fast and the chemical shift is an average of the inside Xe and the gaseous Xe. However, the amount of Xe in the gas is negligible, so the observed chemical shift corresponds to that of Xe inside the crystal. At medium loading, the apparent chemical shift of the adsorbed phase is a result of averaging of the occluded Xe with the significant amount of Xe in the bulk gas and the significant fraction of Xe atoms in Reservoir III; this leads to typical spectral complexity of systems undergoing chemical exchange. The apparent chemical shift in the adsorbed phase would be too low, the apparent chemical shift of the gas signal would be too high, and depending on how fine the powder is, the chemical shift could be dominated by Xe in the intercrystalline space. It is possible to find the true gas phase chemical shift by positioning the sample so that the gas above the sample is partly in the receiver coil.

4 Xe AS AN INTEGRAL PART OF A BIOSENSOR

The hyperpolarized Xe biosensor concept was developed by the Pines group.³³ This is an interesting application of an Xe atom in a flexible cage where exchange with the Xe outside the cage can be significant and is used to advantage. This application exploits the fact that the Xe resonance frequency is strongly shifted when it associates with a molecular cage such as cryptophane-A (see the section “One Xe Atom in a Flexible Cage in Solution”). Such cages can be functionalized with a targeting unit (antibody or ligand) to form xenon biosensors in order to track a specific analyte upon biochemical binding. The biosensor consists of Xe, the cage, the solubilizing linker, and the ligand. The proof of concept was carried out with a biotinylated cage for detecting the protein avidin. Changes in the NMR signal of trapped ^{129}Xe occur upon interaction with the target and provide a powerful tool for spectroscopy and imaging. The mechanism for the sensing action has been established by Monte Carlo averaging of Xe chemical shifts in a cryptophane-A mechanically deformed in molecular dynamics against a protein.¹³ Any mechanical cage distortions that tend to decrease the ratio of the internal volume to the internal surface area of the cage lead to an increased Xe chemical shift (see the section “One Xe Atom in a Flexible Cage in Solution”). The deformation away from the nearly spherical internal space of the cryptophane cage leads to increase in short-distance contacts of Xe with the cage atoms, which in turn leads to a more deshielded average. This mechanism is confirmed by the experimental finding that as the linker is systematically lengthened, the shift upon binding becomes smaller and eventually diminishes to the point that Xe chemical shift in bound and unbound sensors are spectroscopically indistinguishable.³⁴ This is entirely consistent with the mechanism of the Xe shift upon binding being attributable to mechanical deformation of the cage upon buffeting against the protein while tethered.

These sensors link xenon atoms to specific biomolecular targets, the avidin being only a test case, coupling the high sensitivity of hyperpolarized nuclei with the specificity of biochemical interactions. A linker just long enough to permit reaching the recognition site provides maximum chemical shift between bound and unbound sensor for spectroscopic detection. Spectrally resolved magnetic resonance imaging of a selectively targeted xenon biosensor can also be accomplished with good sensitivity to enable the distribution of a micromolar range concentration of the protein to be imaged in a heterogeneous sample.³⁵

Even better than directly observing the caged Xe signal upon binding to the target is the indirect detection of the caged Xe. In this indirect detection, the signal of the large reservoir of free hyperpolarized Xe in the aqueous solution dramatically amplifies the sensor signal via chemical exchange saturation transfer, thus the term HYPER-CEST.³⁶ This method amplifies molecule-specific signals by transferring information from a low-concentration target pool (a biosensor linked to a specific biomolecular target) onto the high-concentration reservoir pool (the hyperpolarized reservoir of Xe in aqueous solution). Xe atoms that spend time within the cryptophane cage quickly return to the solution. This property can be used to transfer a frequency-encoded value of magnetization on the xenon in the cage to the Xe in solution by a selective RF pulse that induces saturation of the Xe spins in the cage. Depending on the exchange rate, hundreds to thousands of caged nuclei per second experience this pulse, resulting in a depletion of the magnetization of free dissolved Xe in the vicinity of the cage. By using the ensemble of free dissolved Xe as a reservoir to detect the flow of saturated spins from the functionalized cage where the magnetization change is encoded, this HYPER-CEST leads to 10⁴ times greater sensitivity than other molecular MRI techniques. Furthermore, this amplification can be tuned by making use of the temperature dependence of the exchange rate between Xe atoms in the biosensor and Xe atoms in the reservoir pool.³⁷ The temperature response is adjustable with lower concentrations of caged Xe providing more sensitivity at higher temperatures. Ultrasensitive detection of the biosensor at 310K has been demonstrated with a concentration of 10 nM.³⁸ Future applications may involve Xe in cages linked to specific antibodies or proteins that have the potential to bind to specific cell membrane receptors.

5 RELATED ARTICLES

Microporous Materials and Xenon-129 NMR; Polarization of Noble Gas Nuclei with Optically Pumped Alkali Metal Vapors.

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Biographical Sketch

Cynthia J. Jameson. b 1937. B.S., 1958, Ph.D., 1963, Illinois. First involved with NMR as a Ph.D. student with Herbert S. Gutowsky working on understanding the NMR chemical shift. Approximately 200 papers in NMR. Research interests: intermolecular effects and dynamic averaging of NMR quantities, spin relaxation in the gas phase, xenon in porous materials.