JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2004; **17:** 787–792
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.795

Stereochemical studies by molecular palpation

E. Locci,[1] K. Bartik,[2] N. Segebarth,[3] M. Luhmer[3] and J. Reisse[2]*

[1]Dipartimento di Scienze Chimiche, Università di Cagliari, Cagliari 09042, Italy
[2]Molecular and Biomolecular Engineering, CP 165/64, Université Libre de Bruxelles, 50 av. F. D. Roosevelt, 1050 Brussels, Belgium
[3]Laboratoire de RMN Haute Résolution, Département de Chimie, CP 160/08, Université Libre de Bruxelles, 50 av. F. D. Roosevelt, 1050 Brussels, Belgium

ABSTRACT: The conformational equilibrium of cyclohexanol was investigated by ^{129}Xe NMR spectroscopy. While the classical NMR approach focuses on a carbon or proton atom belonging to the molecule under investigation, in our ^{129}Xe NMR methodology we use the xenon atom as an external spy. Xenon is able to monitor the interconversion between the axial and the equatorial isomers of cyclohexanol. The conformational equilibrium constant was estimated and is in excellent agreement with the values obtained by ^{1}H and ^{13}C NMR. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: NMR spectroscopy; xenon; conformational equilibrium; cyclohexanol; molecular palpation

INTRODUCTION

Intermolecular interactions play an important role in the chemistry of condensed phases, influencing the properties of the interacting partners such as their molecular structure, spectroscopic properties and reactivity. These interactions are sometimes highly specific and the concept of molecular recognition is then used to describe the relationship between the interacting partners; the host–guest pair in supramolecular chemistry or the drug–receptor pair in medicinal chemistry are examples of systems characterized by specific interactions.[1] We are interested in non-specific intermolecular interactions and in their use to study the equilibria between conformers. We will show that it is possible, using ^{129}Xe NMR spectroscopy with xenon as an external probe, to investigate a chemical equilibrium via intermolecular interactions without perturbing it.

It is safe to assume that if an equilibrium is investigated using NMR spectroscopy, the interaction between the electromagnetic radiation and the chemical system does not modify the equilibrium. This is not necessarily the case if higher energy photons capable of inducing electronic transitions, such as those associated with UV or visible light, are used to investigate the system. If electromagnetic radiation is able to perturb an equilibrium, one would expect intermolecular interactions, which necessarily involve the electronic distributions of the interacting molecules, to perturb the equilibrium. Chemical equilibria are frequently solvent dependent, which means that intermolecular interactions are able to change the standard free energy differences between reactants and products. Such solvent effects on equilibria between stereoisomers have been known for decades.[2] It might therefore appear unrealistic to try to obtain information about a conformational equilibrium using an external probe which must necessarily interact with the conformers in equilibrium. It is in fact possible if the chemical observer (probe) interacts 'gently' and 'identically' with all the molecular species involved in the equilibrium. By this, we mean that specific interactions with any of the molecular species must be avoided. It is also important, and this might at first seems contradictory with the previous requirement, that a physical property of the observer is influenced by interactions with the molecular species under study and that each species has a different effect on the observer so that monitoring of this property allows an accurate and precise quantitative analysis of the equilibrium to be undertaken. In summary, what is needed is a chemical observer that is very sensitive to its environment and is able to 'palpate' the system and give quantitative information about the observed molecular species even if they are in fast equilibrium such as cyclohexanic conformers. Molecular palpation, like medical palpation, can be described as a non-invasive diagnostic method.

Monatomic xenon fulfils all the above-mentioned requirements. Indeed, it is a spherical monatomic species that interacts with other molecules through attractive London and repulsive Pauli energies. These energy terms are essentially non-specific and it is certainly safe to assume that the standard free energy difference between two stereoisomers is essentially the same if xenon is

**Correspondence to:* J. Reisse, Molecular and Biomolecular Engineering, CP 165/64, Université Libre de Bruxelles, 50 av. F. D. Roosevelt, 1050 Brussels, Belgium.
E-mail: jreisse@ulb.ac.be
Contract/grant sponsors: FNRS (LEA CNRS-FNRS).
Contract/grant sponsor: Communauté Française de Belgique; *Contract/grant number:* ARC 2002–2007.

present or not. The xenon NMR parameters, such as the screening constant, depend only on the intermolecular interactions in which that the atom is involved and are furthermore very sensitive to the environment. The ^{129}Xe isotope is characterized by a spin quantum number of $\frac{1}{2}$ and very long relaxation times. In solution, its NMR signal is usually very sharp and screening constant changes of one hertz are detectable. This corresponds to a 10^{-8} change in the screening constant of ^{129}Xe at a resonance frequency of 100 MHz. This means that ^{129}Xe is an extremely efficient observer of its environment. Just by palpating, xenon can detect very tiny differences between molecules with which it is interacting.

We have been involved with xenon NMR since many years.[3–19] Whereas much of the xenon NMR work reported in the literature has been devoted to the characterization of the internal structure of microporous materials such as zeolites and clathrates in the solid state,[20–24] we have used xenon NMR to investigate different systems in solution. In particular, we have used xenon NMR to probe the interaction of xenon atoms with solvent and solute molecules,[6,9,11,25] and to study the interaction between xenon and the hydrophobic cavity of organic host molecules such as α-cyclodextrin,[7] cryptophane-A,[10] and cucurbituril.[15,16] We have used xenon NMR to study protein cavities and have also shown that xenon can differentiate between protein surfaces that differ only in the percentage of charged or polar residues.[17] We have also shown that xenon can be 'chiralized' when it is complexed in a chiral host molecule.[13,14]

We recently reported on the use of ^{129}Xe NMR to monitor a configurational equilibrium in solution between systems that do not complex xenon in a specific site.[19] To our knowledge, ^{129}Xe NMR had, until then, never been used to study systems undergoing a transformation in solution; this type of study had only been undertaken in the investigation of solid materials and in each case specific interactions existed between xenon and several sites in the system under study.[26–28] We chose to study a process that has already been well characterized by other methods: the mutarotation of D-glucose. Our recent work is the first example of the use of what we have now defined as molecular palpation to perform a thermodynamic and kinetic study of an equilibrium between stereoisomers. The two anomers of D-glucose are diastereoisomers that differ only in the configuration at one of their six stereogenic centers. Once the α- or β-anomer of D-glucose has been dissolved in a solvent, epimerization occurs and the concentration of both anomers changes until equilibrium is reached. We monitored this process by measuring, as a function of time, the ^{129}Xe chemical shift in solutions containing initially one or the other of the pure anomers. Our results show that our methodology can indeed be used to study the equilibrium between two molecules that are structurally nearly identical and we were able to derive the thermodynamic and kinetic constants characteristic of the system.

We report here on the use of our ^{129}Xe NMR palpation methodology to study the conformational equilibrium of cyclohexanol. For monosubstituted cyclohexanes, the activation energy for the chair–chair equilibrium is such that at room temperature it is impossible to isolate the conformers and determine their specific properties. Spectroscopic methods characterized by very small timescales, such as IR, Raman or UV spectroscopy, yield spectra that correspond to the sum of the spectra of each conformer (conditions of slow exchange). However, because the extinction coefficients of the two conformers are not known, it is impossible to determine the relative amounts of the two conformers at equilibrium without making use of appropriate model compounds, such as the 4-*tert*-butylcyclohexane derivatives, which exist almost exclusively as one conformer. Implicitly, or explicitly, it is considered that the extinction coefficients are transferable quantities, which in this case means that they are not altered by the presence of the *tert*-butyl group (or any other bulky anchoring group) on the cyclohexane ring. Similar comments are applicable to the 'classical' NMR methodology, known as the Eliel method, used to study the conformational equilibrium of monosubstituted cyclohexane molecules at room temperature. In the case of ^{1}H NMR, for example, it is the chemical shift of the proton on the carbon carrying the substituent that is generally measured (proton in position 1).[29,30] At room temperature, the inversion of the cyclohexane ring is fast on the ^{1}H NMR chemical shift time-scale and the observed chemical shift (δ) is the weighted average of the chemical shift values specific of each interconverting form. Labeling the two chair conformers according to the axial or equatorial position of the substituent, the observed ^{1}H chemical shift can be expressed as follows:

$$\delta = x_e\delta_e + x_a\delta_a \tag{1}$$

where δ_e is the chemical shift of the proton in the equatorial conformer, δ_a is the chemical shift of the proton in the axial conformer and x_e and x_a are the mole fractions of the corresponding conformers. The conformational equilibrium constant can then be estimated using the expression

$$K = \frac{x_e}{x_a} = \frac{\delta_a - \delta}{\delta - \delta_e} \tag{2}$$

One possibility for determining δ_e and δ_a is to investigate the system at a temperature which is sufficiently low so that the rate of conformational inversion is slow on the ^{1}H NMR chemical shift time-scale and the characteristic ^{1}H signals for each individual conformer appear. Their relative intensities provide a direct measure of the equilibrium constant at that temperature. Another possibility is, as in the case of IR spectroscopy, to use 4-*tert*-butyl derivatives as conformationally homogeneous

model compounds since they exist in one conformational form. The direct determination of the chemical shift values specific to each conformer is possible. These values are, once again, considered as transferable quantities, not affected by the presence of the *tert*-butyl group in position 4 on the ring.[30,31] It should be possible, at least in principle, to verify the validity of this procedure by comparing, under conditions of slow exchange and therefore at low temperature, the chemical shifts of each conformation with the chemical shifts of the corresponding *tert*-butyl derivatives. As far as we know, such a comparison has never been performed, probably for experimental reasons. The above-described Eliel method should be applicable to our ^{129}Xe NMR study. The fundamental difference between our ^{129}Xe NMR approach and the classical Eliel method for conformational analysis is that instead of monitoring the chemical shift of a nucleus constituting the cyclohexane system, we are using a spin that is not implicated in the equilibrium: we are using an external spy.

RESULTS AND DISCUSSION

^{129}Xe NMR spectra were recorded at 25 °C for increasing amounts of xenon dissolved in 0.4 mol l^{-1} acetone-d_6 solutions of cyclohexanol, and *cis*- and *trans*-4-*tert*-butylcyclohexanol (see Fig. 1). In these experiments the equilibrium xenon pressure was < 2 atm and, for all the systems studied, a single narrow line was observed in the spectra. The measured ^{129}Xe chemical shift values are shown in Fig. 2 as a function of the total amount of xenon present in the NMR tube. ^{1}H and ^{13}C NMR spectra were also recorded.

The ^{129}Xe NMR spectra indicate that xenon is in fast exchange on the ^{129}Xe chemical shift time-scale between

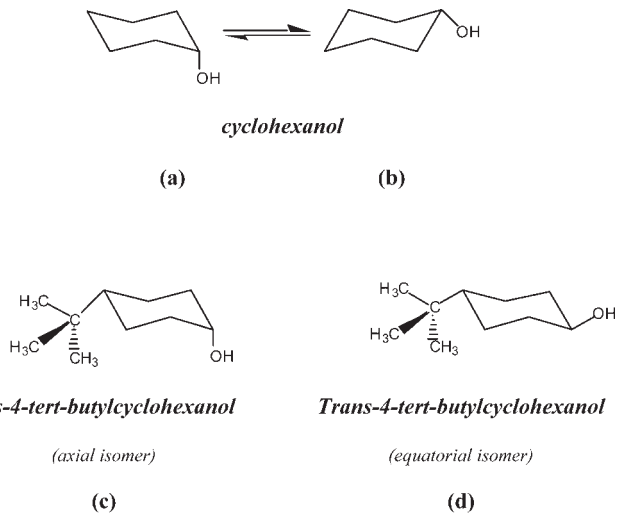

Figure 1. (a), (b) Interconverting conformers of cyclohexanol and (c), (d) favoured conformer of the model compounds

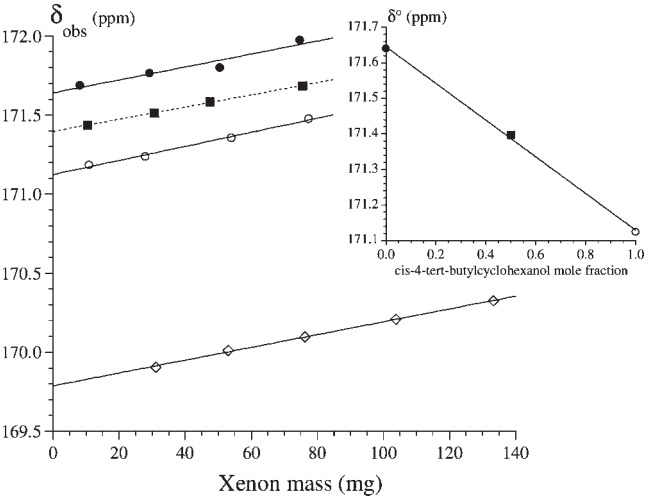

Figure 2. Observed ^{129}Xe chemical shifts for increasing amounts of xenon dissolved in 0.4 mol l^{-1} acetone-d_6 solutions of *trans*-4-*tert*-butylcyclohexanol (●), equimolar mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanol (■), *cis*-4-*tert*-butylcyclohexanol (○) and cyclohexanol (◇). Chemical shifts are measured relative to the ^{129}Xe chemical shift of pure xenon gas extrapolated to zero pressure and are shown as a function of the total mass of xenon present in the NMR tube. In the inset, the ^{129}Xe chemical shift values extrapolated to zero xenon concentration in the solutions of *cis*- and *trans*-4-*tert*-butylcyclohexanol and their equimolar mixture are shown as a function of the component mole fractions

all possible environments in solution: the bulk phase (xenon surrounded by solvent molecules only) and the close environment of the solute molecules which are either the cyclohexane derivatives or other xenon atoms. The two chair conformers, labeled below according to the axial or equatorial position of the hydroxyl group, must be considered as individual species because their lifetime is expected to be much longer than the residence time of xenon in their solvation shell; the xenon atom is not the spectator of the interconversion process itself but samples the resulting equilibrium. (For cyclohexane, the rate of inversion is estimated to be 2×10^5 s^{-1} at room temperature,[32] i.e. a lifetime of 5 μs, whereas the residence time of a water molecule in the solvation shell of xenon dissolved in pure water has been estimated to be 8.2 ps by molecular dynamics simulation.[33]) The observed ^{129}Xe chemical shift can therefore be expressed as follows:

$$\delta_{\text{obs}} = x_{\text{Xe-Solv}}\delta_{\text{Xe-Solv}} + x_{\text{Xe-e}}\delta_{\text{Xe-e}} + x_{\text{Xe-a}}\delta_{\text{Xe-a}} + x_{\text{Xe-Xe}}\delta_{\text{Xe-Xe}} \quad (3)$$

where $x_{\text{Xe}-i}$ and $\delta_{\text{Xe}-i}$ are the mole fraction and the ^{129}Xe chemical shift of xenon in the various environments described above.

The xenon concentration dependence of the ^{129}Xe chemical shift shown in Fig. 2 is a direct consequence of Xe–Xe interactions in solution and is found to be linear. Extrapolating the lines to zero xenon concentration (zero xenon pressure) allows the last term in Eqn (3) to be discarded.

Figure 2 also shows data for xenon dissolved in an equimolar solution of *cis*- and *trans*-4-*tert*-butylcyclohexanol (total concentration 0.4 $mol\,l^{-1}$), which exist almost exclusively in one conformation with the *tert*-butyl group in the equatorial position (the hydroxyl group is in the axial position for the *cis*-isomer and in the equatorial position for the *trans*-isomer; see Fig. 1). ^{129}Xe chemical shifts in this mixture fall exactly half way between the data for the single-component solutions; this is clearly seen in the inset, where the values extrapolated to zero xenon concentration are shown as a function of the component mole fractions. This indicates that xenon exhibits identical affinities for the close environment of both stereoisomers and we can write

$$\frac{x_{\mathrm{Xe-e}}}{x_{\mathrm{Xe-a}}} = \frac{x_{\mathrm{e}}}{x_{\mathrm{a}}} \tag{4}$$

It is likely that this is also the case for the interconverting conformers and an expression analogous to Eqn (1) that relates the observed chemical shift to the mole fractions of the conformers (referred to as x_e and x_a) can then be derived for the extrapolated ^{129}Xe chemical shift:

$$\delta^{\circ} = x_{\mathrm{e}}\delta_{\mathrm{e}} + x_{\mathrm{a}}\delta_{\mathrm{a}} \tag{5}$$

with $\delta_{\mathrm{e}} = \delta_{\mathrm{Xe-Solv}} + (x_{\mathrm{Xe-e}} + x_{\mathrm{Xe-a}})(\delta_{\mathrm{Xe-e}} - \delta_{\mathrm{Xe-Solv}})$ and similarly for δ_a.

The conformational equilibrium constant is then simply given by

$$K = \frac{x_{\mathrm{e}}}{x_{\mathrm{a}}} = \frac{\delta_{\mathrm{a}} - \delta^{\circ}}{\delta^{\circ} - \delta_{\mathrm{e}}} \tag{6}$$

δ_e and δ_a depend on the total concentration of the cyclohexane derivative: the total mole fraction of xenon in the close environment of the cyclohexane derivative, $x_{\mathrm{Xe-e}} + x_{\mathrm{Xe-a}}$, increases with increasing concentration of the derivative.

For the 4-*tert*-butylcyclohexanols, $\delta^{\circ} \approx \delta_a$ for the *cis*-isomer ($x_e \approx x_{\mathrm{Xe-e}} \approx 0$) and $\delta^{\circ} \approx \delta_e$ for the *trans*-isomer ($x_a \approx x_{\mathrm{Xe-a}} \approx 0$). For cyclohexanol, both conformers exist in solution and δ_e and δ_a correspond to the ^{129}Xe chemical shift extrapolated to zero concentration for xenon dissolved in a solution that would contain only the equatorial or the axial conformer, respectively.

The Eliel approach relies on the use of model compounds to estimate the properties characteristic of the interconverting stereoisomers that cannot be isolated. The property measured for the mixture of interconverting stereoisomers must necessarily lie somewhere between the values observed for the model compounds [see Eqns (2) and (6)]. Data given in Table 1 for cyclohexanol and the 4-*tert*-butyl model compounds show that this condition is fulfilled for the chemical shift of the ^{1}H and ^{13}C in position 1 but not for the ^{129}Xe chemical shift extrapolated to zero xenon concentration. Clearly, data obtained by the xenon palpation methodology are affected by the presence of the *tert*-butyl holding group in position 4. This is due, of course, to the extreme sensitivity of xenon. It is obvious that the chemical shift of a xenon atom in the vicinity of one conformation of cyclohexanol and in the vicinity of the corresponding *tert*-butyl derivative will be different: the two molecules are definitively not identical when they are seen from the 'outside' by a xenon atom. The δ° values obtained for the model compounds cannot be directly used in Eqn (6) as an estimate of δ_e and δ_a; they must be corrected for the presence of the anchoring group.

Table 1. Chemical shifts (ppm) for ^{1}H (δ_H) and ^{13}C (δ_C) in position 1 and ^{129}Xe chemical shifts extrapolated to zero xenon concentration (δ°) for cyclohexanol and 4-*tert*-butylcyclohexanols (25 °C; 0.4 $mol\,l^{-1}$ acetone-d_6 solutions)[a]

Parameter	Cyclohexanol	*cis*-4-*tert*-Butylcyclohexanol	*trans*-4-*tert*-Butylcyclohexanol
δ_H	3.50	3.93	3.40
δ_C	69.89	65.30	70.90
δ°	169.79 ± 0.01	171.12 ± 0.01	171.64 ± 0.04
(δ° – $\Delta_{tert\text{-butyl}}$)	—	169.34 (corrected δ_a)	169.86 (corrected δ_e)

[a] Corrected δ_a and δ_e values were obtained by subtracting the contribution to the ^{129}Xe chemical shift of the *tert*-butyl anchoring group present in the model compounds (see text for details). ^{1}H and ^{13}C chemical shifts are given in ppm from TMS and ^{129}Xe chemical shifts are given in ppm from pure xenon gas at zero pressure. The errors on δ° values are fitting errors that result from the linear extrapolation to zero xenon concentration.

^{1}H and ^{13}C NMR chemical shifts are primarily affected by intramolecular effects and are frequently interpreted in term of additive and transferable increments. ^{129}Xe chemical shift changes are solely a consequence of intermolecular interactions and, for dissolved xenon, London and Pauli interactions are dominant. These intermolecular interaction energy terms are usually considered as pairwise additive, suggesting that ^{129}Xe chemical shift can be interpreted in terms of additive group contributions (increments). Because ^{129}Xe chemical shift are solely affected by intermolecular effects, derived group contributions are obviously concentration and solvent dependent and this must be taken into account for the transferability assumption to be valid. We have observed, for example, that in pure *n*-alkanes, *n*-alkanols, *n*-alkanecarboxylic acids and di(*n*-alkyl) ketones the contribution of the methylene (—CH_2—) group is identical once the density of the liquid is properly taken into account.[9] Assuming that ^{129}Xe chemical shifts can be decomposed into additive and transferable group contributions, the correction associated with the presence of a *tert*-butyl group can be determined from the difference between the ^{129}Xe chemical shift in suitably selected reference systems. By this we mean that the systems must resemble the interconverting stereoisomers and the model *tert*-butyl compounds. Furthermore, the data must be measured under identical experimental conditions (temperature, solvent, concentration). The similarity

requirement should also ensure that the xenon affinity for the close environment of the various solutes is identical.

The cyclohexane–*tert*-butylcyclohexane system is, without doubt, similar to the cyclohexanol–4-*tert*-butylcyclohexanols system and is furthermore the simplest that can be selected in order to determine the *tert*-butyl increment. The ^{129}Xe chemical shift in 0.4 mol l^{-1} acetone-d_6 solutions of cyclohexane and *tert*-butylcyclohexane were measured at 25 °C for increasing xenon pressure. As for the other systems, the observed chemical shift increases linearly with xenon concentration. The ^{129}Xe chemical shift extrapolated to zero xenon concentration is found to be 168.232 ± 0.004 and 170.017 ± 0.008 ppm in the cyclohexane and *tert*-butylcyclohexane solutions, respectively. The difference between these figures provides a value of 1.78 ± 0.01 ppm for the contribution of the *tert*-butyl group ($\Delta_{tert\text{-butyl}}$) to the chemical shift. Once this contribution is subtracted from the δ° values obtained for the 4-*tert*-butylcyclohexanols, the δ° measured for cyclohexanol solution at equilibrium falls between the corrected δ_e and δ_a values (Table 1). Using Eqn (6), the conformational equilibrium constant for cyclohexanol dissolved in acetone-d_6 at 25 °C is found to be 6.4, which corresponds to an equilibrium mole fraction for the equatorial conformer of cyclohexanol (x_e) of 0.86. The equilibrium mole fraction determined by the xenon palpation methodology is in excellent agreement with values determined via ^{1}H NMR and ^{13}C NMR (^{1}H results, 0.81 in this study and 0.83 from the work of Lewin and Winstein;[34] ^{13}C result, 0.82 in this study). It is worth pointing out that the agreement between the x_e value for cyclohexanol provided by the xenon palpation methodology and those obtained by ^{1}H and ^{13}C NMR suggests that the assumption regarding the transferability of xenon chemical shift group contributions is valid, at least for ^{129}Xe chemical shifts measured under identical experimental conditions in solutions of cyclohexane derivatives.

CONCLUSIONS

The results presented in this paper, and our results published previously on the mutarotation of D-glucose, show that the palpation method using xenon NMR spectroscopy permits quantitative studies to be carried out for systems out of equilibrium and also for systems at equilibrium. Our choice of rather simple systems, which have been extensively studied by other methods, was aimed at investigating the scope and limitations of the xenon palpation methodology. The palpation method was found to be extremely accurate for the kinetic and thermodynamic study of D-glucose mutarotation because the use of model compounds is not required and no corrective chemical shift increments need to be introduced. In that study, the xenon palpation methodology was even capable of observing H/D isotopic effects.[19] For interconverting conformations in fast equilibrium, the palpation methodology is probably as accurate as many other more 'classical' methods that necessarily also require the use of model compounds and rely on the transferability assumption but which, in contrast to the xenon palpation method, neglect possible effects associated with the presence of an anchoring group in the model compounds. ^{129}Xe NMR presents a major advantage: it generally gives single-line spectra and, even when several lines are observed, their assignment is easy. Coupling patterns are never observed in solution and the screening constant variations depend only on intermolecular interactions. This leads us to conclude that molecular palpation based on xenon NMR could become a tool for conformational studies in systems for which classical methods fail or in complex systems such as peptides or polynucleotides.

EXPERIMENTAL

Natural isotopic abundance xenon gas was purchased from Air Liquide (Belgium). Cyclohexane and *tert*-butylcyclohexane were purchased from Sigma and used without further purification. Cyclohexanol was purchased from Sigma and distilled.

Pure *trans*- and *cis*-4-*tert*-butylcyclohexanol were obtained from a mixture of isomers (60:40 *trans*:*cis*), purchased from Sigma, using chromatographic separation on alumina.[35] The purity of the isolated stereoisomers was assessed by ^{1}H NMR.

Solutions of 0.4 mol l^{-1} cyclohexane derivatives were prepared in a volumetric flask by dissolving precise amounts of the compounds in acetone-d_6. For the ^{129}Xe NMR measurements, 2 ml of solution were placed in a Wilmad high-pressure NMR tube (o.d. 10 mm and i.d. 7.1 mm) of known volume ($\sim$8 ml) and degassed. Increasing amounts of xenon, up to 2 atm were pressurized into the NMR tube at room temperature. The total amount of xenon added was known precisely from the difference between the weight of the sample after xenon addition and the weight of the degassed sample.

^{129}Xe NMR spectra were recorded at 25 °C on a Bruker AMX360 spectrometer (nominal frequency for ^{129}Xe = 99.64 MHz) equipped with a standard 10 mm broadband probe. The chemical shifts were referenced to the chemical shift of pure xenon gas extrapolated to zero pressure (a sealed NMR tube containing xenon dissolved in acetone-d_6 was used as secondary external reference). The temperature was controlled at 25.0 ± 0.1 °C. ^{129}Xe NMR spectra were recorded using a 3 μs pulse, a 5.2 s repetition time and a spectral width of 10 204 Hz. The number of scans recorded varied from spectrum to spectrum so as to obtain good signal-to-noise ratio. The digital resolution was 0.16 Hz per point. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C in 5 mm standard NMR tubes on a Bruker Avance300 instrument. ^{1}H and ^{13}C chemical shifts were referenced to the

chemical shift values of TMS using the solvent signal as secondary internal reference (acetone-d_5, ^{1}H $\delta =$ 2.05 ppm; acetone-d_6, $^{13}CD_3$ $\delta = 29.84$ ppm).[36]

Acknowledgment

This work was supported by the Belgian FNRS (LEA CNRS-FNRS) and the Communauté Française de Belgique (ARC 2002–2007).

REFERENCES

1. Lehn JM. In *Supramolecular Chemistry: Concepts and Perspectives*. Wiley-VCH: Weinheim, 1995.
2. Leffler JE, Grunwald E. In *Rates and Equilibria of Organic Reactions*. Wiley: New York, 1963; 48–56.
3. Reisse J. *New J. Chem* 1986; **10**: 665–672.
4. Luhmer M, Dejaegere A, Reisse J. *Magn. Reson. Chem.* 1989; **27**: 950–952.
5. Dejaegere A, Luhmer M, Stien M-L, Reisse J. *J. Magn. Reson.* 1991; **91**: 362–374.
6. Moschos A, Reisse J. *J. Magn. Reson.* 1991; **95**: 603–606.
7. Bartik K, Luhmer M, Heyes SJ, Ottinger R, Reisse J. *J. Magn. Reson. B* 1995; **109**: 164–168.
8. Luhmer M, Moschos A, Reisse J. *J. Magn. Reson. A* 1995; **113**: 164–168.
9. Luhmer M, Bartik K. *J. Phys. Chem.* 1997; **101**: 5278–5283.
10. Bartik K, Luhmer M, Dutasta JP, Collet A, Reisse J. *J. Am. Chem. Soc.* 1998; **120**: 784–791.
11. Luhmer M, Reisse J. *Prog. Nucl. Magn. Reson. Spectrosc.* 1998; **33**: 57–76.
12. Luhmer M, Goodson BM, Song Y-Q, Laws DD, Kaiser L, Cyrier MC, Pines A. *J. Am. Chem. Soc.* 1999; **121**: 3502–3512.
13. Bartik K, El Haouaj M, Luhmer M, Collet A, Reisse J. *ChemPhysChem* 2000; **1**: 221–224.
14. Bartik K, Luhmer M, Collet A, Reisse J. *Chirality* 2001; **13**: 2–6.
15. El Haouaj M, Luhmer M, Ho Ko Y, Kim K, Bartik K. *J. Chem. Soc., Perkin Trans. 2* 2001; 804–807.
16. El Haouaj M, Luhmer M, Young HK, Kim K, Bartik K. *J. Chem. Soc., Perkin Trans. 2* 2001; 2104–2107.
17. Locci E, Dehouck Y, Casu M, Saba G, Lai A, Luhmer M, Reisse J, Bartik K. *J. Magn. Reson.* 2001; **150**: 167–174.
18. Locci E, Casu M, Saba G, Lai A, Reisse J, Bartik K. *ChemPhysChem* 2002; **3**: 812–814.
19. Locci E, Reisse J, Bartik K. *ChemPhysChem* 2003; **4**: 305–308.
20. Ito T, Fraissard J. *J. Chem. Phys.* 1982; **76**: 5225–5229.
21. Ripmeester JA. *J. Am. Chem. Soc.* 1982; **104**: 289–290.
22. Barrie PJ, Klinowski J. *Progr. Nucl. Magn. Reson. Spectrosc.* 1992; **24**: 91–108.
23. Raftery D, Chmelka BF. In *NMR Basic Principles and Progress*, vol. 30, Blümich B (ed). Springer: Berlin, 1994; 111–157.
24. Ratcliffe CI. *Annu. Rep. NMR Spectrosc* 1998; **36**: 124–208.
25. Luhmer M, Van Belle D, Reisse J, Odelius M, Kowalewski J, Laaksonen J. *J. Chem. Phys.* 1993; **98**: 1566–1578.
26. Boudart M, Ménorval L-C, Fraissard J, Valença GP. *J. Phys. Chem.* 1988; **92**: 4033–4035.
27. Jokisaari J. *Progr. Nucl. Magn. Reson. Spectrosc.* 1994; **26**: 1–26.
28. Nossov AV, Soldatov DV, Ripmeester JA. *J. Am. Chem. Soc.* 2001; **123**: 3563–3568.
29. Reisse J, Celotti JC, Zimmerman D, Chiodoglu G. *Tetrahedron Lett.* 1964; **31**: 2145–2150.
30. Eliel EL, Allinger NL, Angyal SJ, Morrison GA. In *Conformational Analysis*. Wiley: New York, 1965; 152–156.
31. Hanack M. In *Organic Chemistry. A Series of Monographs*, vol. 3, Blomquist A (ed). Academic Press: New York, 1965; 99.
32. Eliel EL, Wilen SH. In *Stereochemistry of Organic Compounds*. Wiley: New York, 1994; 688
33. Schnitker J, Geiger A. *Z. Phys. Chem.* 1987; **155**: 29–54.
34. Lewin AH, Winstein S. *J. Am. Chem. Soc.* 1962; **84**: 2464–2465.
35. Winstein S, Holness NJ. *J. Am. Chem. Soc.* 1955; **77**: 5562–5578.
36. Gottlieb HE, Kotlyar V, Nudelman A. *J. Org. Chem.* 1997; **62**: 7512–7515.