# Determination of the Position of the Conformational Equilibrium of a Trans 1,2-Disubstituted Cyclohexane by NMR Spectroscopy

W

## An Experiment in Physical Organic Chemistry for Undergraduate Students

**Andrei G. Kutateladze\* and Joseph M. Hornback\***

Department of Chemistry and Biochemistry, University of Denver, Denver, CO 80208-2436; \**jhornbac@du.edu*

Multifaceted experiments that combine hands-on lab manipulations, spectroscopic techniques, and molecular modeling by computer provide invaluable experience for undergraduate students. This experiment combines an organic preparation, ^{1}H NMR spectroscopy, and molecular mechanics calculations to determine the position of a conformational equilibrium.

Nuclear magnetic resonance spectroscopy can be used to determine the relative amounts of species present at equilibrium in two ways. Consider the equilibrium between A and B.

$$A \rightleftharpoons B$$

If the equilibrium is slow on the NMR time scale, the intensities of the signals due to A and B can be measured directly. If the equilibrium is fast on the NMR time scale, such as is the case for most conformational equilibria, the chemical shifts, δ, and coupling constants, *J*, are weighted averages of their values for A and B (*1*). If values for the individual species A and B are known, then the mole fraction of A and B in the equilibrium mixture can be calculated.

The experiment summarized here uses coupling constants to determine the percent of the axial–axial (**3aa**) and equatorial–equatorial (**3ee**) conformers of *trans*-1-chloro-2-(2-nitrophenylthio)cyclohexane present in an equilibrium mixture (Scheme I). The cyclohexane derivative (*2*) is prepared by the addition of 2-nitrophenylsulfenyl chloride, **1**, to cyclohexene, **2**, in $CDCl_3$ or $CD_3CN$ in an NMR tube (see scheme below). Reactions of aromatic sulfenyl chlorides with alkenes are known to occur by anti addition (*3*), so the trans isomer of the 1,2-disubstituted cyclohexane is produced. After the ^{1}H NMR spectrum of the product is obtained, the coupling constants for the hydrogens adjacent to the chlorine and sulfur are used to calculate the percentage of each conformer present in the equilibrium mixture.



Scheme I
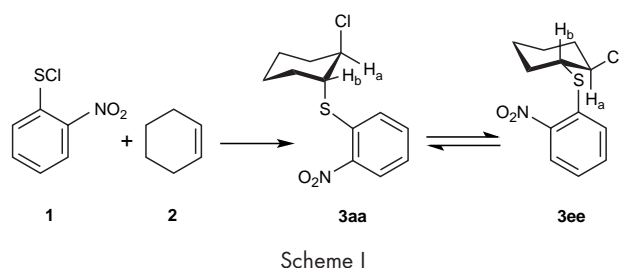
In this experiment students learn about the averaging of NMR data for an equilibrium that is fast on the NMR time scale. They learn that coupling constants depend on the dihedral angle and see how to use the Karplus equation to calculate coupling constants. The experiment provides an opportunity to use a molecular mechanics calculation to determine dihedral angles, if the instructor desires. Students also learn that, unlike the case of *trans*-1,2-dimethylcyclohexane covered in most organic textbooks, where the equatorial–equatorial conformation is much more stable than the axial–axial conformation, larger substituents can destabilize the equatorial–equatorial conformation because of the steric interactions that occur when the groups are gauche, resulting in significant amounts of the axial–axial conformation being present in the equilibrium mixture. Finally, students learn that solvent polarity can affect the position of the conformational equilibrium when the substituents are polar.

The experiment is appropriate for almost any advanced laboratory, including a physical organic chemistry laboratory, a physical chemistry laboratory, or a spectroscopy laboratory. With a brief discussion of the Karplus equation in the laboratory introduction, it could also be incorporated into the organic chemistry laboratory. This experiment could be combined with other experiments that use NMR spectroscopy to investigate the regiochemistry (*4*) and stereochemistry (*3b, 5*) of the addition of aromatic sulfenyl chlorides to alkenes to provide a longer, more comprehensive experiment.

## Experimental Procedure

The reaction is run by adding 0.8 mL of 0.05 M *o*-nitrophenylsulfenyl chloride in $CDCl_3$ to a clean and dry NMR tube using a volumetric pipet. To this is added the calculated amount of cyclohexene (0.004 mL, density = 0.811 g/mL) using a microliter syringe. The tube is capped, shaken, and allowed to stand for at least 30 min. A second NMR tube is prepared using 0.8 mL of 0.05 M *o*-nitrophenylsulfenyl chloride in $CD_3CN$ and the calculated amount of cyclohexene. The reaction is much faster in this solvent and the NMR spectrum can be obtained after a 5-min reaction period.

After the reaction period, the ^{1}H NMR spectrum of each sample is obtained. The multiplet for the hydrogen on the carbon bonded to the chlorine ($H_a$) appears near 4.1 δ and the multiplet for the hydrogen on the carbon bonded to the sulfur ($H_b$) near 3.6 δ. These regions are expanded and the width of each multiplet (the distance, in Hz, between the outermost lines) is determined. This process is repeated for the other solvent.

## Results and Discussion

Both $H_a$ and $H_b$ have three neighboring protons to which they are coupled. The width of each multiplet is equal to the sum of the three coupling constants for that hydrogen. The values that we obtained for the width of the multiplets in $CDCl_3$ were 16.11 Hz for $H_a$ and 16.60 Hz for $H_b$. In $CD_3CN$, the values were 20.99 Hz for $H_a$ and 21.49 Hz for $H_b$.

In order to calculate the equilibrium amounts of the two conformations, the coupling constants in the individual conformations, **3aa** and **3ee**, are needed. Approximate values for these constants can be obtained from the Karplus equation (*6*)

$$J = 7.76 \cos^2 \omega - 1.1 \cos \omega + 1.4$$

where $\omega$ is the dihedral angle between the hydrogens. The need for the dihedral angles provides an opportunity for the instructor to introduce a molecular mechanics calculation into the experiment. We have used the PC Spartan program to calculate the dihedral angles. For those who do not want to do molecular mechanics calculations, idealized values of 180° for axial–axial and 60° for axial–equatorial and equatorial–equatorial dihedral angles or more accurate values (*7*) of 175° for axial–axial, 55° for axial–equatorial, and 65° for equatorial–equatorial dihedral angles can be used. The calculated amounts of **3aa** and **3ee** do not differ significantly no matter which method is used.

The percentages of **3aa** and **3ee** are calculated in the following manner, using $H_a$ as an example. Let $W_{aa}$ be the calculated width, in Hz, for the signal for $H_a$ in **3aa**. Let $W_{ee}$ be the calculated width for the signal for $H_a$ in **3ee**. Let $W_{nmr}$ be the observed width of the signal for $H_a$. And let $x$ be the mole fraction of **3ee** in the mixture; then $1 - x$ is the mole fraction of **3aa** in the mixture. The mole fractions can be calculated from the equation

$$W_{nmr} = x W_{ee} + (1 - x) W_{aa}$$

Upon rearranging, the equation becomes

$$x = \frac{W_{nmr} - W_{aa}}{W_{ee} - W_{aa}}$$

Because of the effect of the differing electronegativities of the chlorine and thioaromatic substituents on the coupling constants, the values for the mole fractions obtained using $H_a$ and $H_b$ are slightly different, so the average of the two values is used. For $CDCl_3$ solvent, the calculated mole fraction of **3ee** is 0.52 using $H_a$ and 0.54 using $H_b$; the average is 0.53. For $CD_3CN$ solvent, the calculated mole fraction of **3ee** is 0.83 using $H_a$ and 0.86 using $H_b$; the average is 0.85. These results show that a significant amount of the axial–axial conformer, **3aa**, is present in $CDCl_3$ as a result of the destabilization of the equatorial–equatorial conformer, **3ee**, by steric and dipole interactions between the substituents. An increase in the amount of the more polar conformer, **3ee**, is observed in the more polar solvent $CD_3CN$.

## Equipment

We employed a 400-MHz NMR instrument for the NMR measurements, but the signals for $H_a$ and $H_b$ are well separated so the required widths of the multiplets can be determined even on a 100 MHz instrument. For the molecular mechanics calculation, we used PC Spartan, available from Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA 92612.

## Chemicals

The following chemicals are needed for this experiment: 2-nitrobenzenesulfenyl chloride, cyclohexene, chloroform-*d*, and acetonotrile-$d_3$.

## Hazards

There are no significant hazards associated with this experiment.

## Acknowledgments

## ᵂSupplemental Material

Supplemental materials for this experiment (student handouts, instructor notes, and sample NMR spectra) are available in this issue of *JCE Online*.

## Literature Cited

1. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; p 641.
2. Hogg, D. R.; Smith, J. H.; Vipond, P. W. *J. Chem. Soc. C* **1968**, 2713–2716.
3. (a) Havlik, A. J.; Kharasch, N. *J. Am. Chem. Soc.* **1956**, *78*, 1207–1210. (b) McGahey, L. *J. Chem. Educ.* **1990**, *67*, 554–555.
4. Silversmith, E. F. *J. Chem. Educ.* **1979**, *56*, 127.
5. Silversmith, E. F. *J. Chem. Educ.* **1982**, *59*, 346.
6. Haasnoot, C. A. G.; DeLeeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.
7. Eliel, E. L.; Wilen, S. H. Op. cit., p 712.