Introduction of a method to analyze 3D structures using homonuclear couplings

Product used : Nuclear Magnetic Resonance (NMR)

Structural analysis by NMR can provide not only a planar molecular structure but also three-dimensional structural information. In this Note, we describe a method for obtaining information on dihedral angles by using ^{1}H-^{1}H coupling constants (J_{HH} values). For example, hydrogen atoms attached to a cyclohexane ring are either located in axial or equatorial positions in respect to the cyclohexane ring (Fig. 1). The dihedral angles between vicinal protons are known to be $\angle H_{ax}$-C-C-$H_{ax} \approx 180^\circ$, $\angle H_{ax}$-C-$H_{eq} \approx 60^\circ$, and $\angle H_{eq}$-C-C-$H_{eq} \approx 60^\circ$. If we look at the Karplus curve shown in Fig. 2, we can see that $^3J_{HH}$ of around 4 Hz can be expected in the case of the dihedral angle of 60° , while $^3J_{HH}$ of around 13 Hz corresponds to the dihedral angle of 180° . In reality, $^3J_{HH}$ values depend on substituents attached to the cyclohexane ring in substituted cyclohexanes, so the analysis is not straightforward, but the basic trend of having a larger *J*-value for a 180° dihedral angle compared to a 60° dihedral angle remains unchanged. Therefore, from the value of $^3J_{HH}$ of the methylene protons, it is possible to differentiate between the dihedral angle of 60° or 180° .

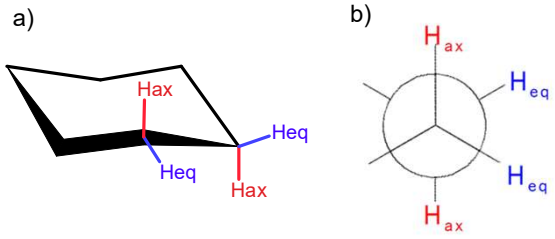


Fig. 1: Stereo configuration of cyclohexane ring a), Newman projection b)

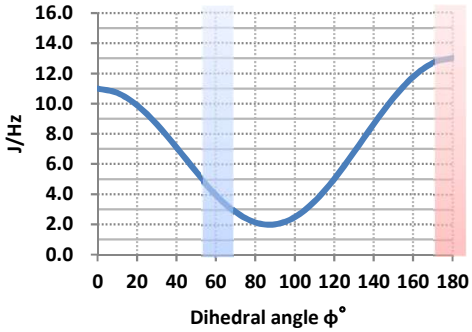
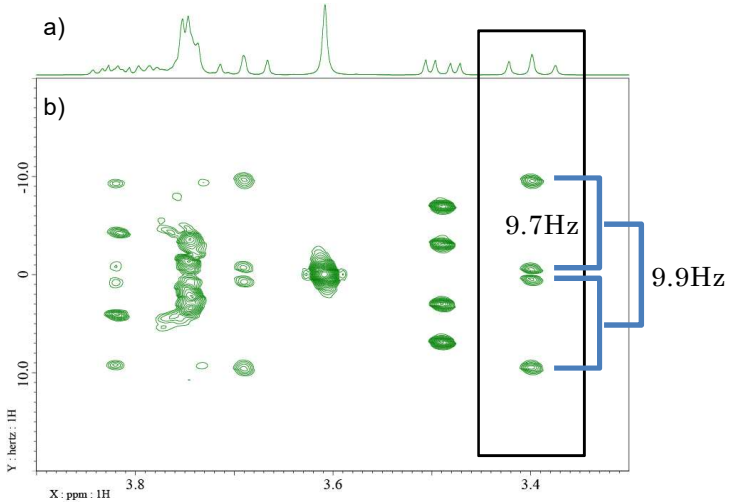


Fig. 2: Karplus curve for cyclohexane ring

J-resolved spectroscopy

As you know, the ^{1}H NMR signal is usually split due to *J*-coupling with nearby ^{1}H, and the *J*-value can be obtained by measuring the distance between the individual peaks in the spectrum. However, it can be difficult to extract reliable *J*-values directly from the ^{1}H spectrum where there is overlap between signals or signals show multiple splittings due to couplings to more than one neighboring hydrogen atom. In such cases, *J*-resolved spectroscopy has been used for many years to address this problem.



The 3.4 ppm signal in Fig. 3 appears to be a triplet in the ^{1}H NMR spectrum a), but the *J*-resolved spectrum b) shows that it is a doublet of doublets (dd), and the *J*-values can be determined accurately. On the other hand, it is not clear which protons couple with this proton. Using the G-SERF [1] (**G**radient-encoded homonuclear **SE**lective **Re**Focusing spectroscopy) experiment, it is possible to determine coupling partners and *J* values of the selected ^{1}H signal at the same time.

Fig. 3: ^{1}H NMR a) and *J*-resolved spectra of sucrose after tilting b).

1) Angew. Chem. Int. Ed. 2010, 49, 3481-3484

G-SERF

The pulse sequence of G-SERF is shown in Fig. 4. In this method, only one proton signal in the spectrum is selectively irradiated at a time. The 2D spectrum then shows only the signals from protons that couple to the selectively irradiated proton. The signals are split by the *J*-coupling in the F_1 (Y) dimension. Fig. 5 shows the G-SERF spectrum of sucrose. The signal at 3.5 ppm, indicated by the blue arrow, is the selectively irradiated signal. The spectrum shows that the proton observed at 3.5 ppm couples with protons observed at 3.7 ppm and 5.35 ppm. The *J*-values are 10.0 Hz and 4.0 Hz, respectively. Note that there are also signals at the positions of other proton signals that do not couple with the selectively irradiated proton and these signals are not split to the F_1 dimension.

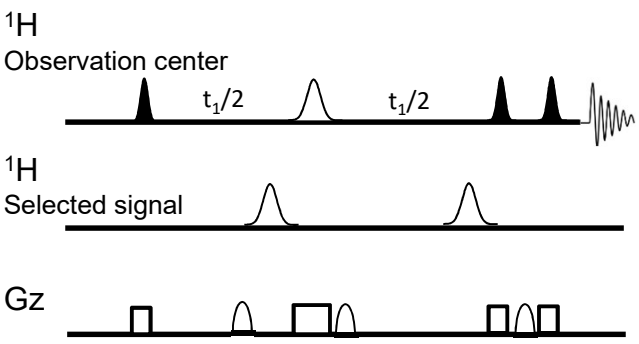


Fig. 4: Pulse sequence of G-SERF

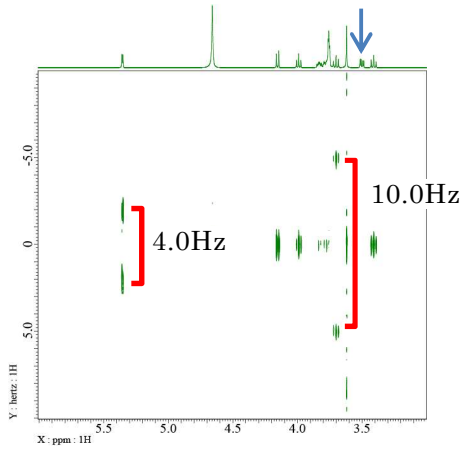


Fig. 5: G-SERF spectrum of sucrose

Clean G-SERF

When analyzing G-SERF spectra, care should be taken when trying to measure small couplings in a crowded region of the ^{1}H spectrum. The signals in the center of the G-SERF spectrum in the F_1 dimension can make it difficult to determine whether there is a real coupling or not. In such a case, the Clean G-SERF experiment [2] is a more useful alternative. This method eliminates the unwanted signals in the center of spectrum, thus making it easy to analyze even very small couplings. On the other hand, the Clean G-SERF experiment is less sensitive than the G-SERF experiment.

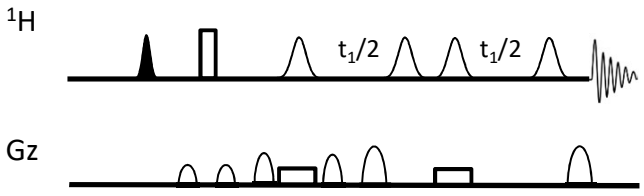


Fig. 6: Pulse sequence of Clean G-SERF

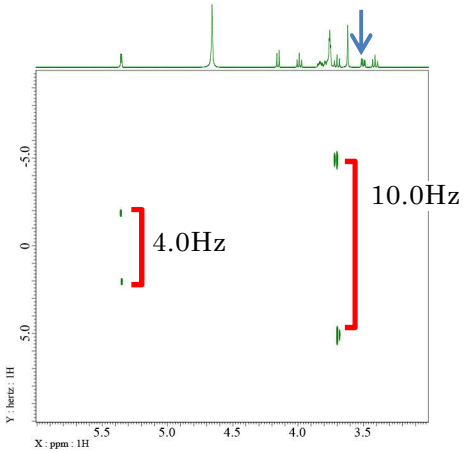


Fig. 7: Clean G-SERF spectrum of sucrose

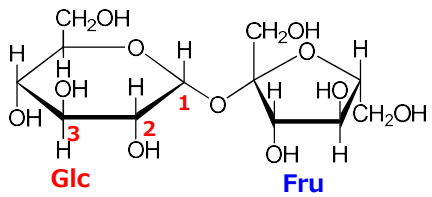


Fig. 8: Structure of sucrose

Fig. 8 shows the structure of sucrose. The proton signal at 3.5 ppm corresponds to H-2 on the glucose ring. From the ^3J-values observed, the dihedral angle between H-1 and H-2 is estimated to be approximately 60°, and the dihedral angle between H-2 and H-3 is approximately 180°, which is consistent with the actual 3D structure.

2) RSC Adv. 2017, 7, 735-741

JEOL Ltd.
3-1-2 Musashino Akishima Tokyo 196-8558 Japan Sales Division Tel. +81-3-6262-3560 Fax. +81-3-6262-3577
www.jeol.com ISO 9001 • ISO 14001 Certified
▼ Local office
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