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Can TMS and DSS be Used as NMR References for Cyclodextrin Species in Aqueous Solution?

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Abstract. Tetramethylsilane (TMS) can be included by β-cyclodextrin (β-CD), and sodium 2,2-dimethylsilapentane-5-sulphonate (DSS) can form inclusion complexes with β- and γ-CD. The NMR chemical shifts are changed considerably as a result of the strong interaction between CD and the guest compound in the inclusion complexes. A downfield shift of as much as 0.63 ppm shift downfield has been observed for the protons of external TMS in CD aqueous solution. In view of this, the question arises of whether TMS and DSS can be used as internal references. DSS in D_2O is suggested as an external reference for aqueous cyclodextrin solution in NMR measurements.

Key words: Cyclodextrin, DSS, inclusion complex, NMR, TMS.

1. Introduction

It is well known that the cavity of cyclodextrin (CD) can include many, often structurally different, guest molecules provided the sizes are suitable for the formation of inclusion complexes in aqueous solution [1–5]. A great number of cyclodextrin inclusion complexes, mainly with aromatic derivatives, have been studied by an array of physical and chemical methods [6–9]. NMR has been found to be a powerful tool for investigating the properties of the inclusion complexes in terms of inclusion, association constants, and molecular structure in solution [10–16]. However, the interaction of cyclodextrin and reference compounds, one of the most fundamental and important points for a correct analysis of the NMR characteristics of cyclodextrin species in aqueous solution, has not fully been discussed in the literature.

Although TMS and DSS are recommended reference compounds for NMR measurements in organic solvents and water, respectively, they may not be suitable for cyclodextrin species, which can form inclusion complexes with the reference compounds. In order to shed light on the possible change of chemical shifts when an inclusion complex is formed between CD and the reference compound, we have investigated the interactions of α-, β- and γ-CD with TMS and DSS using NMR spectroscopy.

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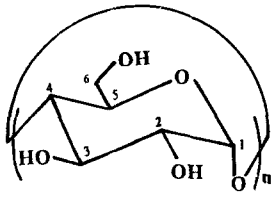
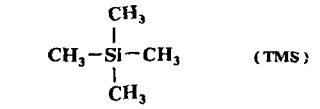
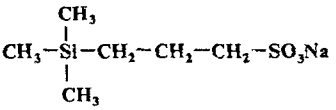


n = 6, α-CD
n = 7, β-CD
n = 8, γ-CD



(TMS)



(DSS)

2. Experimental

2.1. REAGENTS

DSS (99%, Brinkmann Instruments, Inc., New York), TMS (99.9%, Aldrich), D_2O (deuterium atom 100%, Aldrich), α- and γ-CD (Tokyo Kasei) were used as received. β-CD (97%, Suzhou Weijing Plant) was purified by recrystallization three times from distilled water and drying at 86°C *in vacuo* for 24 h before use.

2.2. PREPARATION OF SAMPLES

The NMR samples were prepared by mixing weighed amounts of host and guest compounds in D_2O, and the mixture was exposed to ultrasound at 25°C for 10 min in order to solubilize it. Two capillaries filled with DSS in D_2O and pure TMS, respectively, were sealed as external references.

2.3. NMR MEASUREMENTS

^1H- and ^{13}C-NMR spectra were obtained with a Bruker AM-400 NMR spectrometer. DSS was used as external standard. All measurements were carried out at room temperature.

3. Discussion

When α-CD was used in the experiment, the results indicated that the proton chemical shifts of α-CD in D_2O were unaffected by the addition of both DSS and TMS. This is rationalized by assuming that the small cavity of α-CD cannot accommodate both DSS and TMS, and the interaction between them is so weak that it does not affect the chemical shifts.

On the other hand, when β-CD was used in the experiment, significant changes of the host compound chemical shifts were observed, as well as those of the guest compounds. Figure 1 shows the chemical shifts of the β-CD inner protons as a function of β-CD to DSS molar ratio.

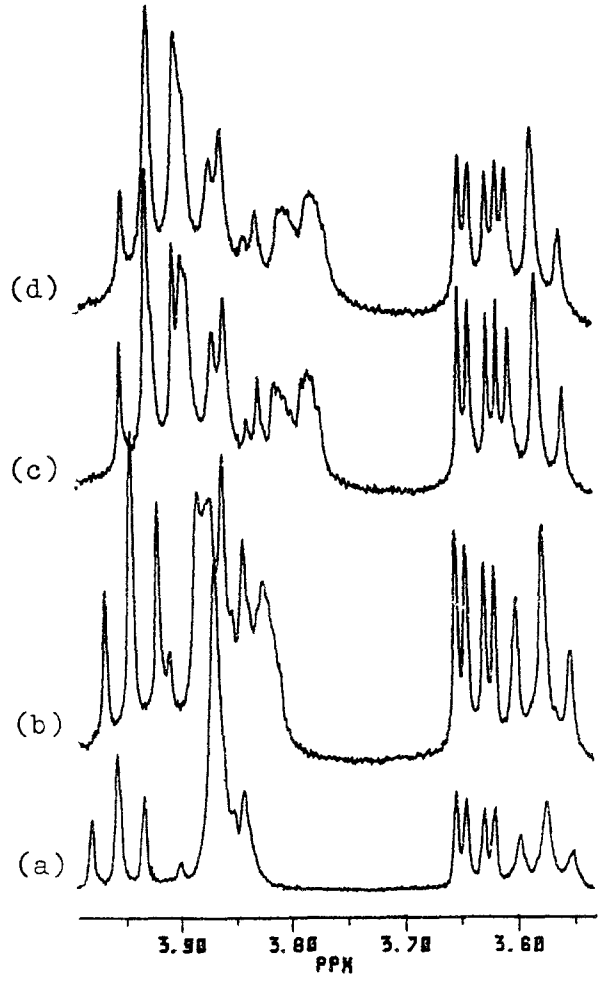


Fig. 1. Partial ^{1}H-NMR spectra of β-CD (8.8×10^{-3} mol/L) alone (a) and in the presence of 3.5×10^{-3} mol/L (b), 8.8×10^{-3} mol/L (c), and 10.5×10^{-3} mol/L (d) DSS in D_2O.

The ^{1}H-NMR spectrum of β-CD in D_2O (Figure 1a) consists of peaks due to five kinds of protons: the H-1 doublet (δ 5.06 ppm, not shown in Figure 1), the H-3 triplet (δ 3.96 ppm), the H-5 and H-6, a strong unresolved broad peak (δ 3.84–3.90 ppm), the H-2 doublets of doublet (δ 3.64 ppm), and the H-4 triplet (δ 3.57 ppm). An upfield shift of δ for H-3 and H-5 of β-CD were observed in the presence of DSS and TMS. A continuous shielding of these protons took place until a 1 : 1 molar ratio between β-CD and DSS was attained (Figure 1c). The chemical shifts of the protons of β-CD in the complex remain unchanged upon further addition of DSS (Figure 1d). Similar observations for other guests were

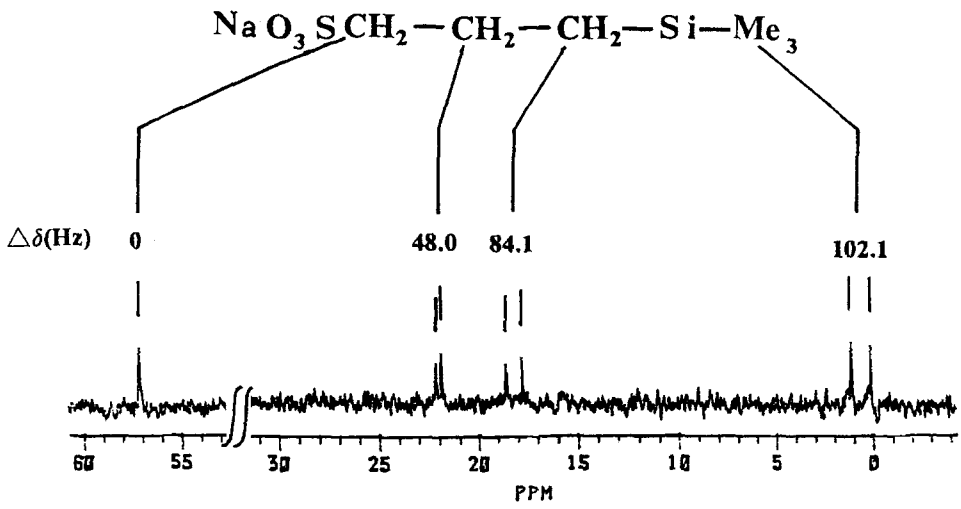


Fig. 2. ^{13}C-NMR spectrum of the DSS (8.8×10^{-3} mol/L) β-CD (8.8×10^{-3} mol/L) inclusion complex in D_2O showing the downfield chemical shift change ($\Delta\delta$) relative to the external DSS reference. $\Delta\delta = \delta_{complex} - \delta_{reference}$.

reported recently [10,17].

It is worth noting that 0.079 ppm (31.6 Hz) and 0.096 ppm (38.4 Hz) downfield shifts for Si-CH_3 protons in the β-CD inclusion complexes with TMS and DSS, respectively, and a 0.03 ppm (12 Hz) downfield shift for CH_2 of the Me_3SiCH_2 group of DSS were also observed. The signal of CH_2 connected to both Me_3SiCH_2 and CH_2SO_3Na groups remains practically unaffected, however, ^{13}C-NMR measurement of the same sample (Figure 2) gave similar results.

The ^{13}C chemical shift change ($\Delta\delta$) of DSS in the β-CD complex reveals that the trimethylsilyl group is deeply embedded in the β-CD cavity. A very strong interaction results in a large $\Delta\delta$ value. Generally, ^{13}C-NMR is not so much affected by the environment as ^{1}H-NMR, but it is sensitive to changes of conformation [18]. Apparently, the $Me_3SiCH_2CH_2$ group of DSS is included within the cavity of β-CD, whereas the CH_2SO_3Na group remains outside. The strength of binding between substrate and cavity [19] was verified by changes in chemical shifts of these groups.

Interestingly, γ-CD can form an inclusion complex with DSS but not with TMS. Figure 3 shows the ^{1}H-NMR spectra obtained from γ-CD (Figure 3a) and its mixture with TMS (Figure 3b) and DSS (Figure 3c) in D_2O. It is seen that the chemical shifts of the γ-CD protons are not affected by the addition of TMS, because the cavity of γ-CD is too large to suit the TMS molecule. In other words, the TMS molecule cannot stay in the γ-CD cavity. On the other hand, the chemical shifts of both γ-CD and DSS showed changes upon mixing. This indicates that a γ-CD–DSS inclusion complex was formed. The results are in agreement with the complexation of β-CD with DSS. The upfield shift for the inner protons of

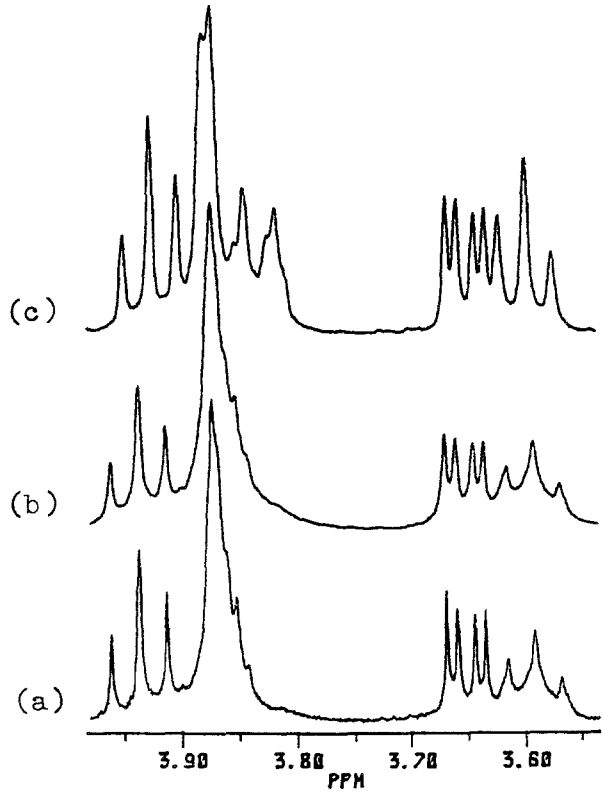


Fig. 3. Partial ^{1}H NMR spectra of γ-CD (4.4×10^{-3} mol/L) in the absence (a) and in the presence of equivalent TMS (b) and DSS (c) in D_2O.

γ-CD was observed in the formation of an inclusion complex of [5-(4-bromo-1-naphthoyl)-pentyl]-trimethylammonium bromide by Turro [20].

TMS is soluble in D_2O with concentration of 2.9×10^{-3} mol/L in the presence of β-CD (8.8×10^{-3} mol/L) through inclusion complex formation at room temperature, but it is insoluble in aqueous solutions of α- or γ-CD, where no inclusion complexes are formed. The present work indicates that the signal of the external TMS reference moves about 0.63 ppm (252 Hz) downfield in aqueous solution relative to DSS external reference, whether the cyclodextrins are present or not. This remarkable change is attributed to the difference in the volume magnetic susceptibilities [21] of TMS and aqueous CD system. On the other hand, the NMR peaks due to both external and internal DSS are exactly identical in the absence of CDs in D_2O. Therefore, DSS is a good choice as NMR external standard for aqueous cyclodextrin species.

Based on the above observations, we feel it is appropriate to conclude that both TMS and DSS cannot be used as the internal reference, and suggest that DSS rather

than TMS be used as the external reference for cyclodextrin species in aqueous solution for NMR measurement.

Acknowledgements

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