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The Use of High-Resolution NMR Spectroscopy in Supramolecular Systems

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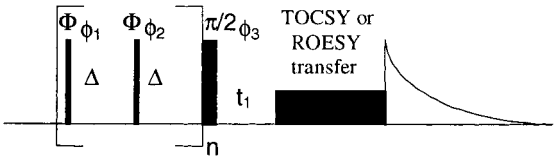
ABSTRACT



Region-selective two-dimensional NMR methods for analysis of Overhauser effects in supramolecular systems are presented here. These experiments are particularly useful when ^{1}H NMR signals are crowded in a small region and conventional techniques cannot be used for such investigations.

The field of supramolecular chemistry,[1−4] which often deals with complicated molecules, suffers from a lack of strategies for elucidation of structures of compounds under investigation. Several new NMR methodologies[5−7] have recently been devised in this quest because X-ray crystallography (the definitive tool for structure determination) is available only for those derivatives which can be crystallized.[8−10] Despite some authoritative efforts by well-known groups,[11−13] there are still some questions that cannot be answered with techniques that are now available. For example, it is difficult to determine through-space interactions (Overhauser effects)[14] among proximate protons if the NMR signals are crowded in a small region, as illustrated in Figure 1 for the cyclodextrin derivative **1**. This situation is exacerbated if, due to low solubility or availability, the concentration of the sample is low. In this Letter, we present a method in which the resolution of spectra can be enhanced and its analysis can be made relatively easy for such compounds. This method uses a combination of region-selective excitation and two-dimensional spectroscopy. We demonstrate the utility of this method using 3-(4-methylamino-3-nitrobenzyl)-β-cyclodextrin (**1**). In **1**, the 7-fold symmetry of cyclodextrin is broken by the selective substitution on one of the α-glucose units. The ^{1}H NMR spectrum contains seven anomeric doublets around 5.1 ppm, well separated from the rest of the skeletal protons. Only two of these anomeric protons are distinguishable (at 5.12 and 5.18 ppm), as shown in Figure 1, and are suitable for a line-selective excitation experiment.[15] Five other signals cannot be studied by a line-selective experiment because of the high overlap among them. Conventional two-dimensional TOCSY[16] and ROESY[17,18]

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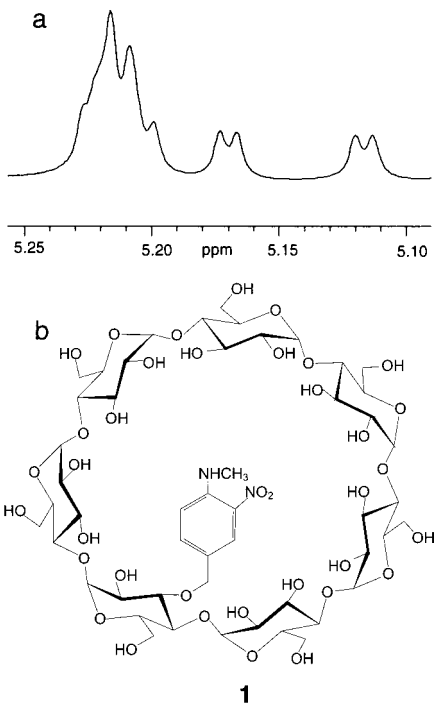

Figure 1. (a) ^{1}H NMR spectrum of the anomeric region and (b) the structure of **1**.

experiments, which are often used to sort out interactions of highly overlapping multiplets, are not conducive for examination of scalar and dipolar interactions of these anomeric protons. As shown in Figures 2 and 3, the low resolution in

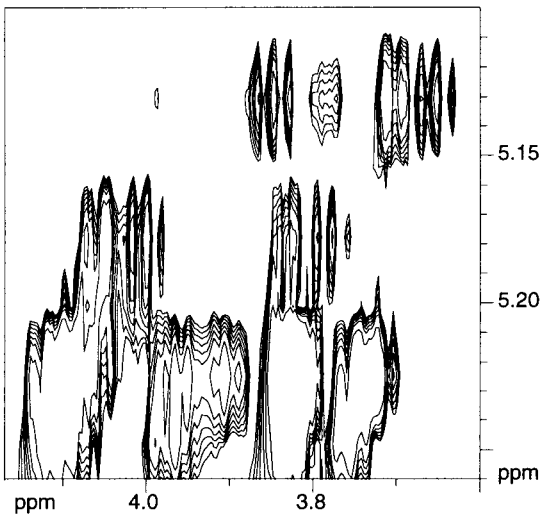

Figure 2. Conventional two-dimensional TOCSY spectrum of **1**.

both detected and incremented dimensions limits the application of these methods to this system and makes these spectra difficult to analyze.

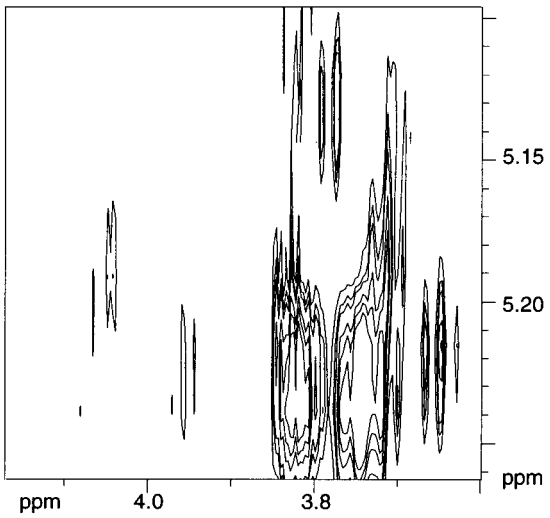

Figure 3. Conventional two-dimensional ROESY spectrum of **1**.

NMR experiments using pulse sequences given in Figure 4 can be used to overcome the problems enumerated above.

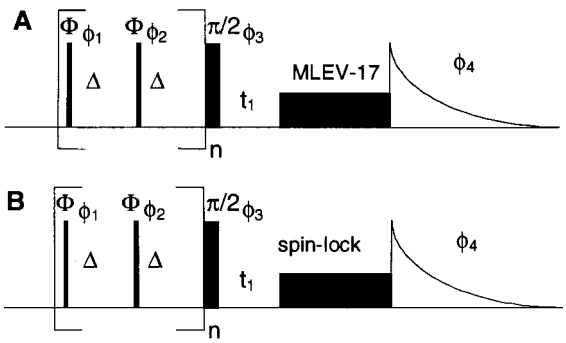

Figure 4. Region-selective two-dimensional pulse sequences. A. TOCSY: $\Phi = 5°$, $\phi_1 = 0$; $\phi_2 = 0, 2$; $\phi_3 = 0, 0$; $\phi_4 = 0, 2$; $\Delta = 150\ \mu$s; MLEV-17 = 105 ms. B. ROESY: $\Phi = 5°$, $\phi_1 = 0$; $\phi_2 = 0, 2$; $\phi_3 = 0, 0$; $\phi_4 = 0, 2$; $\Delta = 150\ \mu$s; the spin-lock pulse strength was 2.44 kHz (90° pulse length was 102.5 μs) with a duration of 500 ms.

These sequences use a region-selective DANTE-Z pulse train applied to excite an approximately 1.5 ppm chemical shift area (around 5.1 ppm) which accommodates the seven anomeric doublets under examination. It effectively reduces the spectral window and makes it possible to acquire the data into high-resolution two-dimensional spectra. The analysis of these high-resolution spectra allows one to obtain structural information on these important signals. Although these experiments alone do not provide sequence-specific assignments, it is possible to identify groups of signals which have interactions with anomeric protons in these spectra.

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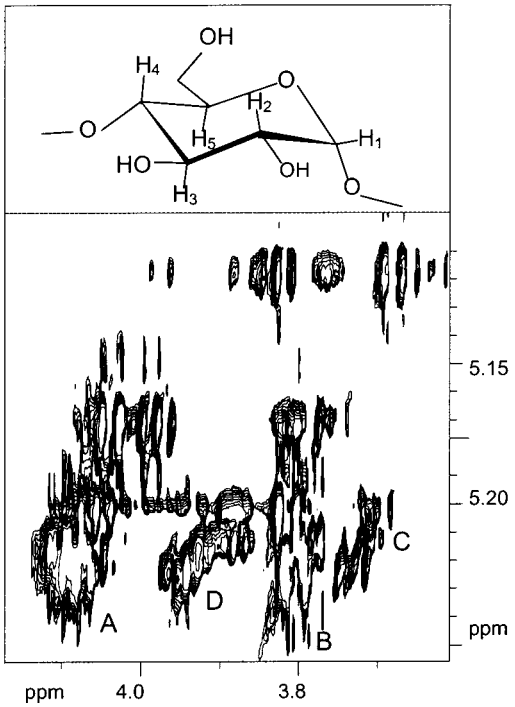

Figure 5. Selective two-dimensional TOCSY spectrum of **1**.

The region-selective two-dimensional TOCSY spectrum is shown in Figure 5. The chemical shift of the H-3 signals is usually higher than that of other skeletal protons, and they have a characteristic triplet structure around 4.1 ppm (Figure 5, region A). The H-2 signals have a characteristic double-doublet structure at lower chemical shifts around 3.8 ppm (Figure 5, region B). The H-5 signals are multiplets (coupled to H-4 and to two H-6 protons) and, therefore, have broad low-intensity signals around 3.9 ppm (Figure 5, region D). The H-4 region (Figure 5, region C) appears to be weak even though these protons are in the axial position and their signals are ideal subjects for TOCSY type magnetization transfers from H-3. However, they have strong dipolar (ROESY) interactions with H-1s in the neighboring glucose units. This mechanism decreases the intensities and distorts the shape of the TOCSY signals for H-4. The distortion of signals in the ROESY spectrum is negligible because the spin-lock power is low and not enough to generate a TOCSY transfer.

The region-selective two-dimensional ROESY spectrum of **1** is given in Figure 6. It shows a different pattern, and three classes of cross-peaks can be identified on the basis of this spectrum. The first class (Figure 6, region A, 3.8 ppm) represents ROE interactions between the equatorial anomeric protons and the axial H-2 protons inside the same glucopyranose unit. The second type of cross-peaks (Figure 6, region B) represents a much weaker interaction between the anomeric protons and H-6 signals in the adjacent glucose unit. The third class of interactions (Figure 6, region C, 3.75 ppm) represents a strong dipolar coupling between the anomeric and the axial H-4 protons in the neighboring glucose rings. These strong interglycosidic interactions

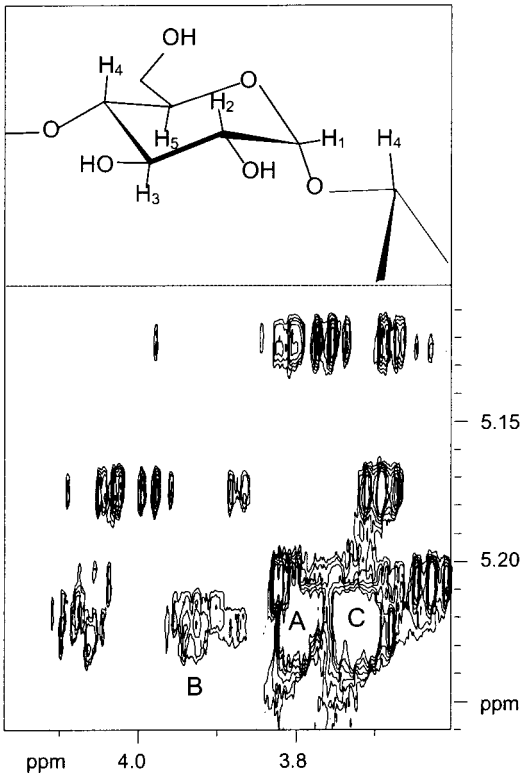

Figure 6. Selective two-dimensional ROESY spectrum of **1**.

between the anomeric protons and the H-4 signals in the neighboring α-glucose units indicate that the two interglycosidic dihedral angles between neighboring α-glucose units (H1−C4 and C1−H4) are small (less than 10°). This conformation of cyclodextrin is similar to the one in the solid phase as elucidated by X-ray crystallography.[19−21] Thus, these region-selective TOCSY and ROESY spectra enable one to extract structural information which is otherwise unavailable.

The method described here, which uses a region-selective DANTE-Z pulse sequence to obtain high-resolution two-dimensional TOCSY and ROESY spectra, can be used to deduce important Overhauser interactions. This method is particularly useful for compounds with low solubility and with regions of crowded ^{1}H NMR signals which makes analysis by conventional methods difficult.

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