Measuring $^{14}N/^{13}C$ Dipole Couplings to Establish Conformation in Unlabeled Materials

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Introduction

Solid-state NMR (SSNMR) provides a powerful technique for determining structure in materials that don't form crystals suitable for x-ray crystallography. Although the ability to determine complete structures from SSNMR is a recent development,[1] numerous structures have now been characterized, primarily by measuring dipole couplings in isotope labeled biomolecules. Unfortunately, general labeling schemes are not available for many other types of molecules and alternative methods are needed that allow characterization of conformation in natural abundance materials. Here, the use of the R-RESPDOR method[2] is explored for measuring $^{14}N/^{13}C$ dipole couplings and conformation in natural abundance materials.

Experimental

All $^{14}N/^{13}C$ R-RESPDOR data for the anticancer drug docetaxel were acquired using a 600 MHz widebore NMR system with a 3.2 mm magic-angle spinning triple-resonance low-*E* probe at the NMHFL. The $^{14}N/^{13}C$ dipolar dephasing curves are fit in the time domain using the universal REDOR curves in Ref. 2 to obtain couplings and to extract the associated distance information.

Results and Discussion

Recently a novel polymorph of the anticancer drug docetaxel was partially characterized in our lab using ^{13}C chemical shift tensor data and computational modeling. However, complete characterization of the sidechain linked to the C13 position has proven challenging. An analysis of the R-RESPDOR data in Figure 1 identifies four ^{13}C sites that experience dipole couplings to the sole ^{14}N site. These data provide distances that establish a key dihedral angle at N–C3'–C2'–C1' of 60° or 300°. Of equal importance is the absence of a coupling between N and C5'. This "systematic absence" indicates an N–C4'–O–C5' dihedral angle of 180°. These data also unambiguously assign the C1', C3' and C4' chemical shifts and provide estimates of the N–C3' and N–C4' bond lengths. A more complete analysis of the sidechain conformation is now possible using ^{13}C chemical shift tensor data because the R-RESPDOR data significantly reduces the number of model conformations that must be considered.[1a]

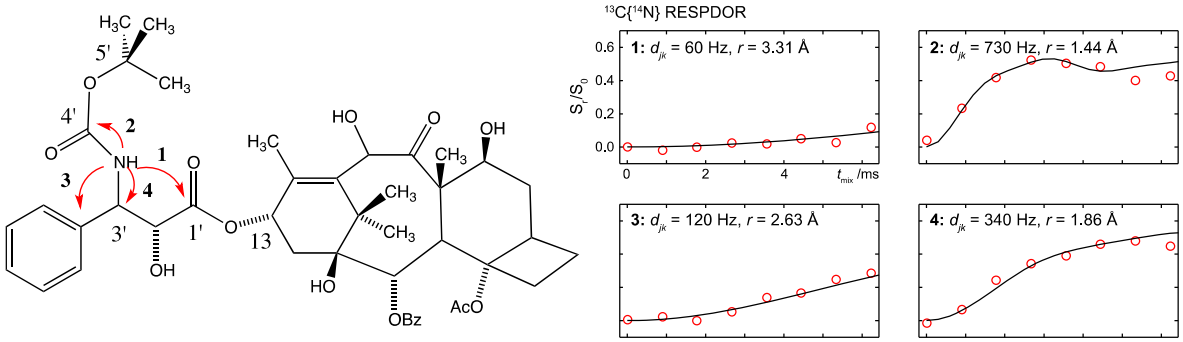

Figure 1. $^{14}N/^{13}C$ R-RESPDOR dipolar dephasing curves (cycle) observed in docetaxel (left), their fitting using the listed dipolar coupling constants and the corresponding $^{14}N/^{13}C$ distances, indicated by numbered arrows in the structure.

Conclusions

The R-RESPDOR analysis of decotaxel demonstrates for the first time that molecular conformations can be established in natural abundance samples using $^{14}N/^{13}C$ distance measurement. The results show that it may be feasible to probe intermolecular couplings between neighboring molecules using the $^{14}N/^{13}C$ R-RESPDOR experiment. Future work will focus on measuring such long contacts to establish lattice structure without diffraction data.

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References

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[2] Gan, Z., Chem. Commun., 4712-4714 (2006).