Solid-State ^{17}O NMR Reveals Energetics of Breaking a Low-Barrier Hydrogen Bond

Lu, J. (Queen's U., Chemistry); Hung, I.; Gan, Z. (NHMFL); Kong, X.; Wu, G. (Queen's U., Chemistry)

Introduction

A low-barrier hydrogen bond (LBHB) refers to a HB in which the potential energy barrier for translational proton transfer between the two heavy atoms is close to or lower than the zero-point energy [1]. In general, the hydrogen atom in a LBHB is located near the mid-point between the two heavy atoms (e.g., O⋯H⋯O or O⋯H⋯N). A LBHB is commonly associated with a very short HB length (r_{OO} < 2.5 and r_{ON} < 2.6 Å) and thus in the literature a LBHB automatically implies a very strong HB. Although the existence of LBHBs in both gas and condensed phases has been firmly established, their role in enzyme catalysis has remained a controversy in the past 20 years [2]. The central issue is whether a LBHB is particularly strong as compared with a regular HB [3]. As direct experimental measurement of HB strength in condensed phases is rather difficult, most arguments are based on high-level computations. In this work, we used solid-state ^{17}O NMR to examine the hydrogen bonding energetics in nicotinic acid (NA) crystals.

Experimental

[1,2-$^{17}O_2$]NA was synthesized at the ^{17}O enrichment level of 20%. Variable-temperature (VT) ^{17}O MAS NMR spectra were obtained at 21.1 T (NHMFL) with a 900 MHz Bruker Avance console and a 3.2 mm home-built MAS ^{1}H-X transmission line probe. The sample temperatures under the 20-kHz MAS condition were calibrated using solid $Pb(NO_3)_2$.

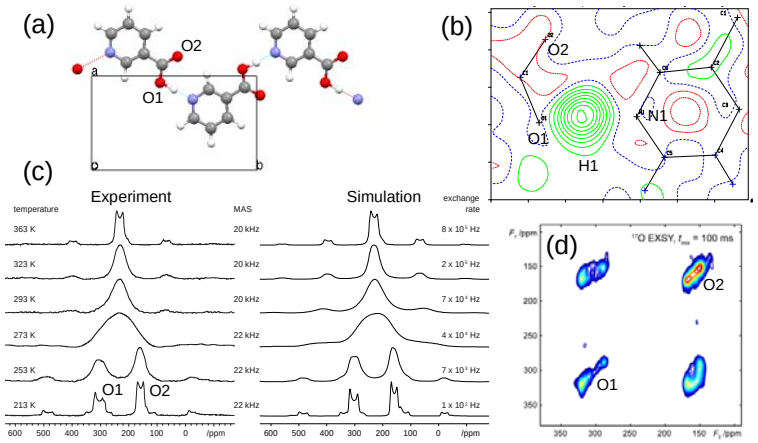

Fig.1 (a) NA molecules form hydrogen bonded zig-zag ribbons along the crystallographic *b* axis. (b) Electron density difference map of NA. (c) Experimental and simulated ^{17}O MAS spectra of [1,2-$^{17}O_2$]NA. (d) 2D EXSY spectrum of [1,2-$^{17}O_2$]NA at 236 K.

Results and Discussion

The intermolecular HB in NA is shown in Fig. 1. While the O⋯N distance of 2.652 Å is relatively long in NA, the Fourier difference map clearly shows that the location of the H1 atom is shifted considerably towards the mid-point of the two heavy atoms, indicative of a LBHB. Both the 1D ^{17}O VT MAS and 2D EXSY spectra suggest that the carboxylate group of NA undergoes a rapid 180º-flip motion in the solid state, which interchanges the chemical environment of O1 and O2. An Arrhenius analysis of the VT ^{17}O NMR data yielded an activation energy (E_a) of 10.3 kcal mol^{-1} for this dynamical process. Interestingly, in order for the carboxylate group to flip, the LBHB must break. Our DFT calculations suggest that, in the absence of any HB, the rotational barrier of the carboxylate group in NA is 3.8 kcal mol^{-1}. Therefore, breaking the LBHB in NA requires as low as 6.5 kcal mol^{-1}. This value falls into the category of weak HBs (2-10 kcal mol^{-1}) [1].

Conclusions

We have shown that the LBHB in NA is not particularly strong. This observation provides strong experimental evidence challenging the concept that a LBHB must be a strong HB. The solid-state ^{17}O dynamic NMR approach provides unique information about HB energetics that are difficult to obtain with other experimental techniques.

Acknowledgements

This work was supported by NSERC of Canada. A portion of this work was performed at the National High Magnetic Field Laboratory, which is supported by National Science Foundation Cooperative Agreement No. DMR-1157490, the State of Florida, and the U.S. Department of Energy.

References

[1] Jeffrey, G. A., An Introduction to Hydrogen Bonding, Oxford University Press, New York (1997).
[2] a) Cleland, W. W., Biochemistry, **31**, 317-319 (1992); b) Gerlt, J. A., *et al.,* J. Am. Chem. Soc., **115**, 11552-11568 (1993).
[3] Perrin, C. L., Acc. Chem. Res., **43**, 1550-1557 (2010).