Solid-State ^{17}O NMR of Pharmaceutical Compounds: Salicylic Acid and Aspirin

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Introduction

Salicylic acid (SA) and *o*-acteylsalicylic aicd (Aspirin) are important pharmaceutical compounds. Similar to many carboxylic acids, SA and Aspirin molecules form centrosymmetric hydrogen bonded dimers in the crystal lattice. In these carboxylic acid dimers, the concerted double proton transfer across two symmetry-related hydrogen bonds is usually associated with a double-well potential, which generally is asymmetric due to crystal packing; see Fig. 1. While there have been intense investigations of proton dynamics in carboxylic acid dimers [1], solid-state ^{17}O NMR has not been utilized in this area. In this work, we used solid-state ^{17}O NMR to determine the asymmetry of the double-well potential in SA and Aspirin.

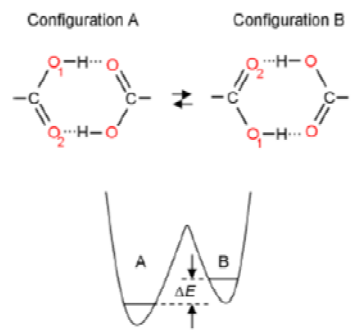

Fig.1. Proton dynamics and the associated double-well potential curve in SA and Aspirin dimers.

Experimental

[1,2-$^{17}O_2$]SA and [1,2-$^{17}O_2$]Aspirin were 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. Sample temperatures under the 20-kHz MAS condition were calibrated using solid $Pb(NO_3)_2$ in a temperature range of 140-360 K.

Results and Discussion

As seen from Fig. 2, while the spectra of SA exhibit very little temperature dependence, those for Aspirin are highly temperature dependent. In particular, as the temperature is increased, the two peaks observed for Aspirin move gradually towards each other. In addition, the ^{17}O quadrupole coupling parameters for the two oxygens also change considerably as a function of temperature. Using the averaging procedure described in the literature [2], together with the CASTEP computed ^{17}O NMR tensors for configurations A and B, we were able to analyze the observed VT ^{17}O MAS spectra and obtain an accurate value of ΔE for Aspirin, 3.0 ± 0.5 kJ/mol. For SA, as no obvious temperature dependence was observed, only a lower limit for ΔE can be estimated, ΔE > 10 kJ/mol. These ΔE values were in agreement with the results of plane-wave DFT computations, ΔE = 3.7 and 17.8 kJ/mol for Aspirin and SA, respectively.

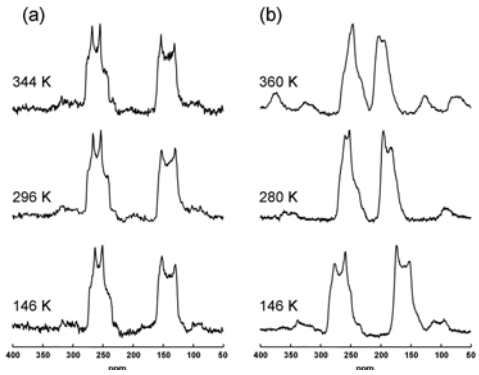

Fig.2. VT ^{17}O 20-kHz MAS NMR spectra of (a) [1,2-$^{17}O_2$]SA and (b) [1,2-$^{17}O_2$]Aspirin at 21.1 T (NHMFL).

Conclusions

We demonstrated that it is necessary to consider the concerted double proton transfer in SA and Aspirin in order to compare experimental and computed ^{17}O NMR tensors for hydrogen-bonded carboxylic acid dimers. We showed that a careful analysis of VT ^{17}O NMR spectra can provide an accurate measure of the energy asymmetry in the double-well potential. A complete account of this work has been published [3].

Acknowledgements

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References

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[2] Meier, B.H., *et al*., J. Chem. Phys., **76**, 767−774 (1982).
[3] Kong, X., *et al*., J. Phys. Chem. B, **117**, 9643−9654 (2013).