

Hydrogen/Deuterium-Isotope Effects on NMR Chemical Shifts and Symmetry of Homoconjugated Hydrogen-Bonded Ions in Polar Solution

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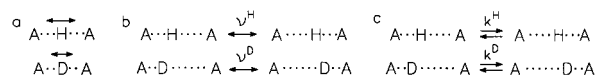
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The understanding of the relation between the NMR parameters and the nature of strong or low-barrier hydrogen bonds in polar but aprotic environments is crucial for the elucidation of enzymatic reaction pathways using NMR spectroscopy.¹ Of special interest are homoconjugated symmetric ions where the loss of the molecular symmetry induced by intermolecular interactions can be probed by measuring H/D-isotope effects on the NMR chemical shifts without complications arising from equilibrium isotope effects. Furthermore, systems with intermolecular hydrogen bonds are not exposed to steric strain as systems with intramolecular hydrogen bonds and are, therefore, better models of interactions of flexible amino acid side chains. The development of solvents which allow one to obtain NMR spectra at low temperatures has improved the requirement of this method to reach the slow hydrogen bond exchange regime even for small model systems. For example, the Freon mixture CDF₃/CDF₂Cl (1:2) is liquid down to 90 K,² and its dielectric constant increases from about 20 at 170 K to about 40 at 100 K^{2e} which provides a convenient way to vary the solvent polarity.

Using this methodology we have been able to measure the H/D-isotope effects on multinuclear NMR chemical shifts of tetra-n-butylammonium (TBA) hydrogen diacetate and of bis-2,4,6-trimethyl pyridinium (bis-collidinium) tetrafluoroborate as models for the interactions of the side chains of aspartic acid and histidine. The choice of these ions was motivated by the analogy to interacting amino acid side chains such as aspartic acid or histidine in active sites of enzymes.³ For comparison we have reexamined also the [FHF]⁻ and the hydrogen maleate anion with TBA as counterion, for which low-temperature data have not yet been reported.

To facilitate the discussion we summarize in Scheme 1 the expected H/D-isotope effects on the geometry of linear symmetric hydrogen bonded systems. We remind that these effects arise from zero-point vibrations, whereas equilibrium geometries are isotope-independent within the Born–Oppenheimer approximation. Case (a) depicts the symmetric single-well potential where the deuteron is more confined to the hydrogen bond center than the proton

Scheme 1



due to a smaller amplitude of the zero-point stretching vibration. This effect leads to a small contraction of the heavy atom distance upon deuteration, as was demonstrated theoretically^{4a} and experimentally^{4b,c} for [FHF]⁻. Case (b) corresponds to a symmetric double-well potential with delocalized protons and deuterons oscillating between the two wells with the tunnel frequency ν . In other words, the proton and or deuteron eigenstates are delocalized eigenstates of the vibrational Hamiltonian. As compared to the proton, the deuteron is shifted away from the hydrogen bond center.^{5a,b,d} In addition, the heavy atom distance of the deuterated bridge is larger than in the protonated bridge. The geometric isotope effects in case (c) are similar, but now intra- and intermolecular interactions have destroyed the symmetry of the proton potential leading to a proton localization in either the left or the right well. Both forms interconvert via a rate process characterized by a rate constant k .

In Figure 1a the low-temperature NMR signals of [FHF]⁻ and [FDF]⁻ are depicted. As expected, they are split by scalar coupling with a normal ratio of $^1J_{\text{FH}}/^1J_{\text{FD}}$. A primary low-field shift $\rho\Delta(\text{H/D}) \equiv \delta(\text{FDF}) - \delta(\text{FHF}) = 0.32$ ppm and a secondary high field fluorine shift $^2\Delta\text{F(D)} \equiv \delta(\text{FDF}) - \delta(\text{FHF}) = -0.37$ ppm are observed. These values are independent of temperature in the range between 110 and 170 K, and they are almost identical to those obtained previously^{5a,c} for acetonitrile between 250 and 300 K. The new information obtained here is then that geometry of [FHF]⁻ is almost independent of the solvent polarity and temperature and that the symmetry of the ion is only slightly perturbed by intermolecular interactions. This finding is in agreement with a single well potential as depicted in case (a). The main source of the observed H/D-isotope effects on the ¹H and ¹⁹F chemical shifts is that the deuteron is more effectively confined to the hydrogen bond center as compared to the proton, as indicated by the double arrow in Scheme 1a. This interpretation is in agreement with our recent findings of the dependence of ¹H and ¹⁹F chemical shifts of (FH)_nF⁻ clusters upon the hydrogen bond geometry^{5d} and with the discussion of single well potentials in intramolecular hydrogen bonds by Forsen et al.^{5a,b,e}

In the case of the maleate anion (Figure 1b) we observe a primary isotope effect of $\rho\Delta(\text{H/D}) = \delta(\text{ODO}) - \delta(\text{OHO}) = 0.08$ ppm, which is slightly larger than the value of +0.03 ppm reported in ref 5a (-55 °C, CD₂Cl₂) and a vanishing value in ref 6a (+25 °C, CDCl₃). The secondary and tertiary isotope effects on the carbon chemical shifts are found to be $^2\Delta\text{C(D)} = -0.07$ ppm for C1, and $^3\Delta\text{C(D)} = -0.05$ ppm for the C2 (signal not shown), which exceed the experimental error of about 0.01 ppm. These results have been also explained⁶ in terms of case (a), but the solvent and temperature conditions start now to play a role.

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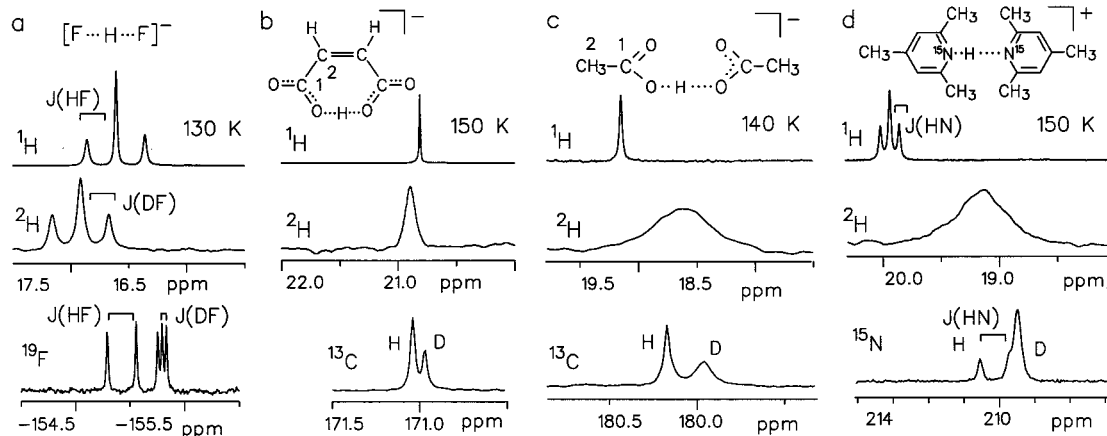


Figure 1. Low-temperature NMR spectra (Bruker AMX 500.13 MHz ^1H frequency) of homoconjugated ions dissolved in the Freon mixture $\text{CDF}_3/\text{CDF}_2\text{Cl}$ (1:2) at different deuterium fractions in the hydrogen bond sites. (a) tetrabutylammonium (TBA) hydrogen difluoride [$\delta(\text{FHF}) = 16.60$ ppm, $\delta(\text{FHF}) = -154.96$ ppm, $^1J(^1\text{H}-^{19}\text{F}) = 124$ Hz, $^1J(^2\text{H}-^{19}\text{F}) = 19$ Hz]. (b) TBA maleate [$\delta(\text{OHO}) = 20.82$ ppm, $\delta(\text{C1}(\text{H})) = 171.05$ ppm, $\delta(\text{C2}(\text{H})) = 137.56$ ppm]. (c) TBA hydrogen bis-acetate, 90% ^{13}C -enriched in the carboxylic groups [$\delta(\text{OHO}) = 19.17$ ppm, $\delta(\text{C1}(\text{H})) = 180.19$ ppm]. (d) 95% ^{15}N -enriched bis-collidinium tetrafluoroborate [$\delta(\text{NHN}) = 19.93$, $\delta(\text{NHN}) = 210.20$ ppm, $^1J(^1\text{H}-^{15}\text{N}) = 40$ Hz]. Chemical shifts references $(\text{CH}_3)_4\text{Si}$ for ^1H and ^{13}C , $(\text{CD}_3)_4\text{Si}$ for ^2H , CFCl_3 for ^{19}F and solid $^{15}\text{NH}_4\text{Cl}$ for ^{15}N .

The spectra of hydrogen diacetate, 90% enriched with ^{13}C at C1, are shown in Figure 1c. We observe a large upfield shift for C1 upon deuteration, $^2\Delta\text{C}(\text{D}) = -0.20$ ppm, as illustrated in Figure 1c. The proton signal resonates around 19.2 ppm, and exhibits a substantial negative value of the primary isotope effect, $^p\Delta(\text{H}/\text{D}) = -0.53$ ppm.⁷ The different sign of this effect as compared to $[\text{FHF}]^-$ indicates qualitatively that these results are in agreement with cases (b) or (c). The ^{13}C chemical shift and H/D isotope effect on the chemical shift pattern observed for the bis-acetate anion constitutes, therefore, a very useful diagnostic tool for this kind of interaction. We note that the line width of the deuteron signal in the bis-acetate anion is much larger as compared to the maleate ion, although the sample temperatures were not much different. Therefore, this finding indicates a much larger quadrupole coupling constant and hence a larger electric field gradient at the ^2H nucleus in the case of the bis-acetate as compared to maleate.⁸ This observation supports the above interpretation in terms of cases (b) or (c).

Finally, we present in Figure 1d multinuclear NMR signals of the homoconjugated bis-collidinium cation. The proton signal also resonates at very low field, and a primary high-field shift of -0.81 ppm is observed upon deuteration. The deuteron line width again indicates a substantial electric field gradient at the deuteron. The ^1H signal consists of a triplet with a $^1J(^1\text{H}-^{15}\text{N})$ coupling constant of 40 Hz which is somewhat smaller than approximately half the value of about 85 Hz typical for protonated pyridines.⁹

(7) A value of $^p\Delta(\text{H}/\text{D}) = -0.64$ ppm has been assigned by Fenn, M. D.; Spinner, E. *J. Phys. Chem.* **1984**, *88*, 3993 to the hydrogen diformate anion in aqueous solution at room temperature. However, the chemical shift of the hydrogen bond proton, 14.12 ppm is not in agreement with the 20.2 ppm observed for this ion in Freon solution.^{2a}

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A single averaged ^{15}N signal is observed for the two nitrogen atoms which experiences a considerable negative secondary isotope shift of $^1\Delta\text{N}(\text{D}) = -0.70$ ppm upon deuteration. This shift indicates that the N–D distance is smaller than the N–H distance. Thus, these findings are compatible with either cases (b) or (c). This interpretation is supported by the value of $^1J(^1\text{H}-^{15}\text{N})$ which should be much smaller if case (a) were realized.¹⁰ The observation of a sharp averaged nitrogen signal indicates that the tunnel frequencies or rate constants must be larger than 10^5 s^{-1} even at 110 K.

We conclude that important details of the structures of a wide set of homoconjugated ions can be obtained by the study of H/D isotope effects on hydrogen bond NMR chemical shifts at low temperatures. Even a strong increase of the solvent polarity at low temperatures does not lead to an asymmetrization of the hydrogen bonds of $[\text{FHF}]^-$ and of the maleate anion. Further experimental and theoretical studies are in progress to reproduce the experimental results in a more quantitative way, and to explore the border between case (b) and case (c).

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