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Formation of Charge Relay Chains between Acetic Acid and Pyridine Observed by Low-Temperature Nuclear Magnetic Resonance

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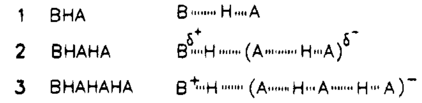
For a long time it has been supposed that strong hydrogen bonds play a dominant role in enzyme catalysis.[2−5] Especially important are so-called "charge relay chains" which consist of a sequence of linearly hydrogen bonded molecules with mobile protons. It is thought that the catalytic activity of the chains consists of a facile formation of a nucleophile A^- according to

$$\mathrm{B\cdots H{-}X\cdots H{-}A} \underset{\leftrightarrow}{\overset{\rightleftarrows}{\text{or}}} \mathrm{B{-}H^{+}\cdots X^{-}\cdots H{-}A} \underset{\leftrightarrow}{\overset{\rightleftarrows}{\text{or}}} \mathrm{B{-}H^{+}\cdots X{-}H\cdots A^{-}} \quad (1)$$

There are many open questions concerning the action of charge relay chains. For example, are the tautomers in eq 1 separated by an energy barrier, as indicated by the symbol $\rightleftarrows$, or do they represent canonical structures of a nonclassical species, as indicated by $\leftrightarrow$? Is the motion of the two protons and the heavy atoms of the hydrogen bonds coupled? Since transition states can be probed only indirectly, e.g., by the determination of kinetic H/D isotope effects,[3,4] the development of charge relay model systems,[3−5] which can be studied spectroscopically, is desirable.

The model system proposed here consists of acetic acid (AH) and pyridine-^{15}N (B) dissolved in halocarbons. Such solutions exhibit extremely broad and complicated IR absorption bands, which are often difficult to interpret.[6,7] Here we employ NMR spectroscopy, a method which has proved to be useful for the study of hydrogen bond dynamics[8−11] and proton transfer.[12] NMR experiments have already been performed on solutions of carboxylic acids and pyridine in organic solvents, but only in the fast hydrogen bond and proton exchange regime.[8,9] In order to reach the slow hydrogen bond exchange regime where well-resolved NMR signals are observed for different hydrogen-bonded complexes, the temperature has to be lowered below 120 K. For this purpose, special solvents have to be employed which remain liquid at these temperatures.[10,11] Here we employed a 2:1 mixture of $CDClF_2$ and CDF_3[13] and performed measurements at 109 K. Various hydrogen-bonded complexes between AH and B (Scheme 1) were identified which give rise to well-resolved NMR signals.

Scheme 1



The low-field part of the 500 MHz ^1H NMR spectra of solutions of AH and B at 109 K are shown in Figure 1a−d. The spectra only depend on the concentration ratio C_{AH}/C_B but are almost independent of the absolute concentrations. At $C_{AH}/C_B = 0.7$, a singlet is observed at 17.7 ppm (Figure 1a). This signal has to be assigned to the hydrogen bond proton B*H*A of the 1:1 complex **1** (Scheme 1). The scalar coupling constant $J_{BHA} \approx 0$, where B represents the ^{15}N nucleus of pyridine. As C_{AH}/C_B is increased, two new lines appear at 20.8 and 15.6 ppm exhibiting an intensity ratio of 1:1 as expected for B***H***AHA and BHA***H***A of the 1:2 complex **2** (Figure 1b). The low-field signal is split into a doublet because of scalar coupling with the ^{15}N nucleus of pyridine, characterized by the average coupling constant $J_{BHAHA} = 63$ Hz. As C_{AH}/C_B is further increased (Figure 1c), two new lines appear at 18.9 and 14.8 ppm, which we assign to B***H***AHAHA and BHA***H***AHA/BHAHA***H***A of **3**. The observed equivalence of the latter two protons either is accidental or arises from a fast intramolecular exchange process. The B***H***AHAHA signal is split into a doublet characterized by $J_{BHAHAHA} = 85$ Hz. Finally, as C_{AH}/C_B is once more increased, the fraction of **3** increases and a new broad signal belonging to the carboxylic protons of the cyclic dimer appears at 13.5 ppm $(A\mathit{H})_2$ (Figure 1d). Evidence for formation of a 1:4 complex was not obtained. As the temperature is raised, all lines shift strongly, broaden, and coalesce into a single line, indicating a fast interconversion of all complexes. In this regime the spectra greatly depend on C_{AH} and C_B.

The ^{15}N NMR spectra at 109 K are consistent with these results. As shown in Figure 1e,f, the pyridine signal is shifted

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(13) The solvent mixture freezes below 90 K. It was prepared from $CDCl_3$ via fluorination with $SbF_3/SbCl_5$ by modifying a recipe proposed by Siegel and Anet: Siegel, J. S.; Anet, F. A. L. *J. Org. Chem.* **1988**, *53*, 2629. The modification consisted in carrying out the reaction at 100 °C in an autoclave at higher pressures instead of 1 atm and in using a larger ratio of $SbF_3/CDCl_3$. The solvent was handled on a vacuum line which also served to prepare the samples.[12a] The solvent composition was checked by NMR.

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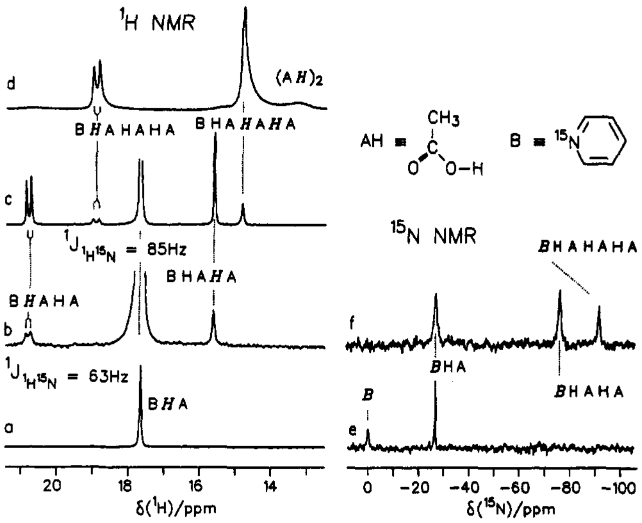

Figure 1. 500 MHz ^{1}H NMR (a−d) and 50.69 MHz ^{15}N NMR spectra with gated ^{1}H decoupling (e, f) of solutions of pyridine-^{15}N (B) (95% ^{15}N enrichment) and of acetic acid (AH) in a mixture of $CDClF_2/CDF_3$ (2:1) at 109 K; (a−d) internal standard TMS; (e, f) external standard neat nitromethane at room temperature. C_{AH} and C_B concentrations (determined at room temperature): 0.05 M, 0.07 M (a); 0.05 M, 0.05 M (b); 0.02 M, 0.015 M (c); 0.06 M, 0.015 M (d), 0.016 M, 0.027 M (e), 0.055 M, 0.03 M (f). Italic letters are used for the assignment of the nuclei to the NMR signals. Number of scans: 64 (a−d), 256 (e, f). Recycle delay: 4 s (a−d), 15 s (e, f). Pulse widths: 50° (a−d), 30° (e, f).

by −28 ppm to high field upon the formation of **1**, by −76 ppm upon the formation of **2**, and by −83 ppm in the case of **3**.[14] Under the same conditions, we observe an upfield shift of −86 ppm for the case of a typical ionic complex, i.e., pyridine hydrochloride.

The observation that $J_{BHA} \approx 0$ indicates the formation of a molecular 1:1 complex according to Scheme 1, where the proton is located close to the oxygen atom. On the other hand, the value of $J_{BHAHAHA}$ compares well with the value of 89 Hz, which we observe under similar conditions for pyridinium hydrochloride; for aqueous acid solutions a value of 90.5 ± 1 Hz has been reported.[15] Thus, in **3** an acid proton is almost fully transferred to B. The lower value of J_{BHAHA} then indicates an intermediate situation. In other words, in the aprotic environment employed here, the "activity" or rather the "proton-donating power" of acetic acid increases with the chain size.

In terms of a conventional proton transfer equilibrium involving a barrier and a fixed hydrogen length, one should expect the B*H*AHA proton signal to be located somewhere between the B*H*A and the B*H*AHAHA signals, but this is not the case here. Therefore, the substantial low-field shift experienced by the proton in B*H*AHA as compared to B*H*A and B*H*AHAHA is a strong evidence for an *increase of the hydrogen bond strength as the proton is partially transferred*, as illustrated schematically in Scheme 1. Therefore, if the B*H*AHA proton experiences an energy barrier for its motion, it must be very small. The ^{15}N chemical shifts are consistent with this interpretation.

In conclusion, the experiments described reveal that pyridine and acetic acid form in halocarbons 1:1, 1:2, and 1:3 hydrogen-bonded complexes **1**−**3** (Scheme 1), where a proton is gradually shifted from acetic acid to pyridine. In particular, the 2:1 complex **2** represents an efficient charge relay chain subject to large time dependent dipole moment fluctuations. Currently, experiments are performed on partially deuterated samples which reveal H/D isotope effects on the chemical shifts of the hydrons and ^{15}N atoms across several hydrogen bonds. So far, only intramolecular isotope shifts have been observed, to our knowledge.[16] These results, which will give further insights into the questions raised above, will be presented and discussed in a forthcoming paper.

Acknowledgment. We thank one of the referees for drawing our attention to ref 5a, where the role of strong hydrogen bonds in enzyme catalysis is discussed, similarly as in refs 5b,c. The support of the Stiftung Volkswagenwerk, Hannover, the Fonds der Chemischen Industrie, Frankfurt, and the International Science Foundation (Grant R 28000) is gratefully acknowledged.

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[14] The ^{15}N chemical shifts reported can be converted into the nitromethane scale or the NH_2Cl scale[15] using the values of −69.2 or 293.7 ppm for pyridine−^{15}N dissolved in $CDCl_3$ at room temperature.

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[16] See issue of *J. Mol. Structure*, May 1994, on "Isotope Effects".