

# Nuclear Scalar Spin – Spin Coupling Reveals Novel Properties of Low-Barrier Hydrogen Bonds in a Polar Environment

Nikolai S. Golubev,<sup>\*,[a,b]</sup> Ilja G. Shenderovich,<sup>[a,b]</sup> Sergei N. Smirnov,<sup>[b]</sup>  
Gleb S. Denisov,<sup>[b]</sup> and Hans-Heinrich Limbach<sup>\*,[a]</sup>

**Abstract:** The structure of the hydrogen bridge  $^{19}\text{F}\cdots\text{H}\cdots^{15}\text{N}$  in the acid–base complex  $\text{A}\cdots\text{H}\cdots\text{B}$  formed by HF and [ $^{15}\text{N}$ ]2,4,6-trimethylpyridine in  $\text{CDF}_3/\text{CDF}_2\text{Cl}$  has been studied between 112 K and 200 K by low-temperature, multinuclear NMR spectroscopy. For the first time scalar spin–spin coupling between all three nuclei of a hydrogen bridge is observed. This bridge exhibits a two-bond coupling constant  $^2J_{^{19}\text{F}^{15}\text{N}}$  of about 96 Hz, which is larger than the

one-bond coupling constants  $^1J_{\text{H}^{15}\text{N}}$  and  $^1J_{^{19}\text{F}\text{H}}$ . The latter are strongly dependent on temperature. The function  $^1J_{\text{H}^{15}\text{N}} = f(^1J_{^{19}\text{F}\text{H}})$  cannot be described in terms of a conventional equilibrium between the molecular and the zwitterionic form, but only with the intermediate forma-

tion of very strongly hydrogen-bonded complexes of the type  $\text{A}^{\delta-}\cdots\text{H}\cdots\text{B}^{\delta+}$  that exhibit a vanishing or very small barrier for the proton motion. Here, the difference between the covalent bond and the hydrogen bond disappears even in the case of a polar solvents, as indicated by the large value of  $^2J_{^{19}\text{F}^{15}\text{N}}$ . Implications for the mechanism of proton transfer and of acid–base catalyzed enzyme reactions in a locally aprotic but polar environment are discussed.

**Keywords:** acidity • basicity • hydrogen bonds • NMR spectroscopy • scalar coupling • solvent effects

## Introduction

Very short and strong hydrogen bonds found in complexes of the type  $\text{A}^{\delta-}\cdots\text{H}\cdots\text{B}^{\delta+}$ ,  $\text{A}^{\delta-}\cdots\text{H}\cdots\text{A}^{\delta-}$ , or  $\text{B}^{\delta+}\cdots\text{H}\cdots\text{B}^{\delta+}$ , also called low-barrier hydrogen bonds, have been studied for a long time.<sup>[1–17]</sup> Their possible role in acid–base catalysis of organic and enzymic reactions has been postulated by Kreevoy et al.,<sup>[3]</sup> Schowen et al.,<sup>[4]</sup> Frey,<sup>[5]</sup> Mildvan<sup>[6]</sup> and us.<sup>[7]</sup> Recently, the concept of transition state stabilization through strong hydrogen bonding has been questioned.<sup>[8, 9]</sup> In particular, it was argued on theoretical grounds<sup>[8]</sup> that a low-barrier hydrogen bond that is stable in the gas phase or in the solid state may be unstable in a polar solvent. In this case specific solvation could lead to charge localization and a fast equilibrium between two asymmetric tautomers,<sup>[7]</sup> that is,  $\text{A}-\text{H}\cdots\text{B} \rightleftharpoons \text{A}^-\cdots\text{H}-\text{B}^+$ , and thus exhibit weaker hydrogen bond energies. Other theoretical studies<sup>[1c, 15–17]</sup> are consistent

with the presence of low-barrier hydrogen bonds in polar media. New experiments that can help to solve this problem are, therefore, desirable.

In the past years some of us have shown that liquid state NMR below 150 K is a fruitful method in order to study experimentally low-barrier hydrogen bonds in polar media.<sup>[10–13]</sup> This is because under these conditions hydrogen-bond exchange may be slow within the NMR time scale so that individual properties of low-barrier hydrogen bonds can be studied. As a suitable solvent we have used mixtures of the freons  $\text{CDF}_3$  and  $\text{CDF}_2\text{Cl}$ , which are liquids down to 90 K.<sup>[10, 11]</sup> These mixtures are very polar especially at low temperature, as the dielectric constant increases drastically from about six at room temperature to forty at 90 K.<sup>[12]</sup> In recent studies of complexes of [ $^{15}\text{N}$ ]pyridine with various acids<sup>[13]</sup> evidence for the formation of a continuous distribution of stable complexes  $\text{A}-\text{H}\cdots\text{B} \rightleftharpoons \text{A}^{\delta-}\cdots\text{H}\cdots\text{B}^{\delta+} \rightleftharpoons \text{A}^-\cdots\text{H}-\text{B}^+$  was obtained, in which  $\text{A}^{\delta-}\cdots\text{H}\cdots\text{B}^{\delta+}$  exhibits the shortest distance between A and B, and in which the zwitterionic complexes were favored at low temperatures.

In this paper, we provide further NMR evidence for this interpretation in a novel way, by observation for the first time all scalar spin–spin couplings of the three nuclei of a hydrogen bridge. The system studied is the 1:1 complex between [ $^{15}\text{N}$ ]2,4,6-trimethylpyridine ([ $^{15}\text{N}$ ]collidine) and HF in  $\text{CDF}_3/\text{CDF}_2\text{Cl}$  (Figure 1). A pyridine derivative was chosen because of similar proton–acceptor properties to the imidazole ring of histidine, but avoiding complications arising from

[a] Prof. Dr. H.-H. Limbach, Dr. N. S. Golubev, I. G. Shenderovich  
Institut für Organische Chemie, Freie Universität Berlin  
Takustrasse 3, D-14195 Berlin (Germany)  
Fax: (+49) 30-838-5310  
E-mail: limbach@chemie.fu-berlin.de  
E-mail: golubev@chemie.fu-berlin.de

[b] Dr. N. S. Golubev, I. G. Shenderovich,  
S. N. Smirnov, Prof. Dr. G. S. Denisov  
Institute of Physics, St. Petersburg State University  
198904 St. Petersburg (Russian Federation)  
E-mail: gsd@gsd.usr.pu.ru

the donor properties of the latter. The collidine derivative was chosen because it is much easier to label with  $^{15}\text{N}$  than pyridine itself. The formation of a low-barrier hydrogen bond in pyridine acid complexes was expected from our previous work<sup>[10–13]</sup> and a crystallographic study on the pyridine/HF complex that indicated a very short  $\text{N}\cdots\text{F}$  bond length of 2.47 Å.<sup>[2b]</sup> From the NMR standpoint, the system studied has the advantage that all three nuclei of the hydrogen bridge  $^{19}\text{F}\cdots\text{H}\cdots\text{N}$  exhibit a spin of one half; this avoids complications from quadrupole relaxation of other nuclei such as  $^{14}\text{N}$  and  $^{17}\text{O}$ . Unexpectedly, we were able to observe not only

**Abstract in German:** Die Struktur der  $^{19}\text{F}\cdots\text{H}\cdots\text{N}$  Wasserstoffbrücke im Säure-Base-Komplex  $\text{A}\cdots\text{H}\cdots\text{B}$  aus HF und  $[\text{N}^{15}]\text{2,4,6-Trimethylpyridin}$  in  $\text{CDF}_3/\text{CDF}_2\text{Cl}$  wurde zwischen 112 und 200 K durch Mehrkern-Tiefemperatur-NMR-Spektroskopie untersucht. Zum ersten Mal wurden skalare Spin-Spin-Kopplungen zwischen allen drei Kernen einer Wasserstoffbrückenbindung beobachtet. Die Brücke ist durch eine Kopplungskonstante  $^2J_{^{19}\text{F}^{15}\text{N}}$  von ca. 96 Hz gekennzeichnet, die größer ist als die stark temperaturabhängigen Kopplungskonstanten  $^1J_{\text{H}^{15}\text{N}}$  und  $^1J_{^{19}\text{F}\text{H}}$ . Die Funktion  $^1J_{\text{H}^{15}\text{N}} = f(^1J_{^{19}\text{F}\text{H}})$  läßt sich jedoch nicht mit einem konventionellen Gleichgewicht zwischen der molekularen und der zwitterionischen Form beschreiben, sondern nur mit der intermediären Bildung von sehr starken Wasserstoffbrücken-Komplexen des Typs  $\text{A}^{\delta-}\cdots\text{H}\cdots\text{B}^{\delta+}$  mit verschwindender oder sehr kleiner Barriere für die Protonenbewegung. In diesen Komplexen verschwindet der Unterschied zwischen der kovalenten Bindung und der Wasserstoffbrückenbindung, selbst im Fall von polaren Lösungsmitteln, wie der große Wert von  $^2J_{^{19}\text{F}^{15}\text{N}}$  zeigt. Folgerungen für den Mechanismus von Protonenübertragungen und Säure-Base-katalysierten Enzymreaktionen in lokaler aprotischer polarer Umgebung werden diskutiert.

#### Abstract in Russian:

**РЕЗЮМЕ:** Методом многоядерной ЯМР спектроскопии в интервале 112–200 К изучена структура комплексов с водородной связью  $^{19}\text{F}\cdots\text{H}\cdots\text{N}^{15}$ , образованных молекулами HF и 2,4,6-триметилпиридина- $^{15}\text{N}$  в растворе в  $\text{CDF}_3/\text{CDF}_2\text{Cl}$ . Впервые наблюдалось скалярное спин-спиновое взаимодействие между всеми тремя ядрами водородного мостика. В этом мостике константа взаимодействия через две связи  $^2J_{^{19}\text{F}^{15}\text{N}}$ , равная 96 Гц, больше констант взаимодействия через одну связь  $^1J_{\text{H}^{15}\text{N}}$  и  $^1J_{^{19}\text{F}\text{H}}$ . Обе последние константы сильно зависят от температуры. Зависимость  $^1J_{\text{H}^{15}\text{N}} = f(^1J_{^{19}\text{F}\text{H}})$  не может быть описана на основе предположения об обычном равновесии между молекулярной и цвиттерионной формами, но согласуется с представлением об образовании промежуточного комплекса с очень сильной водородной связью  $\text{A}^{\delta-}\cdots\text{H}\cdots\text{B}^{\delta+}$  и очень низким или совсем отсутствующим барьером для движения протона. В таком комплексе исчезает различие между ковалентной и водородной связями, даже в полярном растворителе, что следует из большой величины  $^2J_{^{19}\text{F}^{15}\text{N}}$ . Обсуждается значение этих результатов для понимания механизма перехода протона и кислотно – основных каталитических ферментативных реакций в локальном апротонном полярном окружении.

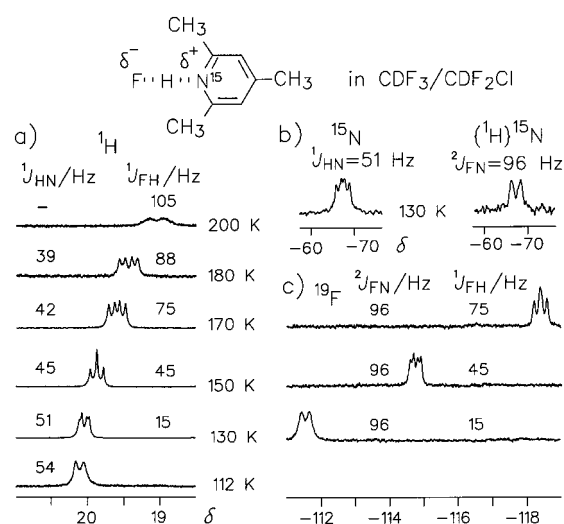


Figure 1. a)  $^1\text{H}$  NMR signals of the hydrogen-bond proton of the 1:1 complex between  $[\text{N}^{15}]\text{collidine}$  and HF in the  $\text{CDF}_3/\text{CDF}_2\text{Cl}$ . Sample **a**: 10-fold excess of collidine. b) Normal and  $(^1\text{H})^{15}\text{N}$  decoupled  $^{15}\text{N}$  spectrum at 130 K of sample **b**, containing a 7-fold excess of collidine. In this sample additional hydrogen-bonded complexes are observed by  $^1\text{H}$  NMR. c)  $^{19}\text{F}$  spectra of sample **a**. The margin of error of the coupling constants (only absolute values are given) is  $\pm 3$  Hz for the  $^1\text{H}$  NMR measurements below 200 K,  $\pm 5$  Hz for the  $^{19}\text{F}$  and  $^{15}\text{N}$  measurements, because of short transverse relaxation, and  $\pm 10$  Hz for the  $^1\text{H}$  spectrum at 200 K, because of line broadening due to hydrogen-bond exchange.

couplings between  $^1\text{H}$  and  $^{19}\text{F}$  and  $^1\text{H}$  and  $^{15}\text{N}$ , but also a large coupling between  $^{15}\text{N}$  and  $^{19}\text{F}$ , which indicated the covalent character of the hydrogen bridge. In the following, after a short experimental section, the results are presented and their implications for the nature of hydrogen bonding and enzymic catalysis in polar media discussed.

## Experimental Section

Collidine enriched with the  $^{15}\text{N}$  isotope (96%) was synthesized from trimethylpyrylium tetrafluoroborate and  $[\text{N}^{15}]\text{ammonium chloride}$ .<sup>[18]</sup> The solvent mixture  $\text{CDF}_3/\text{CDF}_2\text{Cl}$ , whose composition varied between 1:2 and 1:3, was prepared as described previously.<sup>[10–13]</sup> In order to prepare the NMR samples a small amount of 40% HF in water was added to an excess of the base (between 1:5 and 1:15) dissolved in acetone in a teflon flask. Water and acetone were removed by repeated azeotropic distillation in the presence of increasing amounts of dichloromethane. The latter was then removed in vacuo leaving an oily product that was placed in an NMR sample tube equipped with a teflon needle valve (Wilmad, Buena, N.Y.) and cooled to 77 K in order to prevent reaction with the glass. The tube was connected to a high vacuum line and the solvent—dried over alumina—was added by vacuum transfer. The NMR spectra were then recorded on a Bruker AMX 500 spectrometer (Berlin). All coupling constants reported are absolute values as no attempt was made to determine their signs.

## Results

Several samples were prepared with different HF/collidine ratios. As the NMR measurements were made at low temperatures in the slow hydrogen-bond exchange regime, variation of the concentrations did not substantially affect the chemical shifts and coupling constants, although the samples exhibited differences in line broadening at higher temperatures due to

the onset of hydrogen-bond exchange. In Figure 1 some multinuclear NMR spectra of the 1:1 complex between HF and [<sup>15</sup>N]collidine in CDF<sub>3</sub>/CDF<sub>2</sub>Cl are depicted, in the presence of a large excess of the base. At 112 K the hydrogen-bond proton of sample **a** (10-fold excess of collidine) exhibits a signal at about  $\delta = 20.2$ , which shifts to higher field when temperature is increased. This finding indicates the formation of a strong hydrogen bond that weakens somewhat with increasing temperature. The signal at 112 K is split into a doublet by coupling with <sup>15</sup>N and exhibits a one-bond coupling constant of  $^1J_{\text{H}^{15}\text{N}} \equiv ^1J_{\text{HN}} = 54$  Hz. This constant slightly decreases at higher temperatures, at which an additional coupling  $^1J_{^{19}\text{F}\text{H}} \equiv ^1J_{\text{FH}}$  gradually appears. These assignments are confirmed by <sup>15</sup>N NMR (Figure 1b) and <sup>19</sup>F NMR (Figure 1c). For the former sample **b** was used, containing a higher total concentration of the complex and a smaller excess (7-fold) of the base. The higher concentration was necessary because of a better signal-to-noise ratio; in order to control <sup>15</sup>N-signal line-broadening due to hydrogen-bond exchange the excess of the base was reduced. Even after <sup>1</sup>H decoupling a doublet survived in the <sup>15</sup>N spectrum of this sample (Figure 1b, right side), which can then only be assigned to a scalar coupling across the bridge to  $^2J_{^{19}\text{F}^{15}\text{N}} \equiv ^2J_{\text{FN}}$ . This coupling was found again in the <sup>19</sup>F NMR spectra, which is most easily seen in the 112 K spectrum, in which  $^1J_{\text{FH}}$  is small. We note that the coupling constant  $^1J_{\text{FH}}$  increases and  $^1J_{\text{HN}}$  decreases monotonously when temperature is increased, whereas  $^2J_{\text{FN}}$  remains constant within the margin of error. At higher temperatures  $^1J_{\text{HN}}$  is no longer resolved and only  $^1J_{\text{FH}}$  survives; however, the line broadens rapidly and the doublet structure disappears because of various hydrogen-bond-exchange processes.

In Figure 2 we have plotted the coupling constant  $^1J_{\text{HN}}$  as a function of  $^1J_{\text{FH}}$ . We obtain a relation that is linear within the margin of error. It is tempting to interpret this dependence in

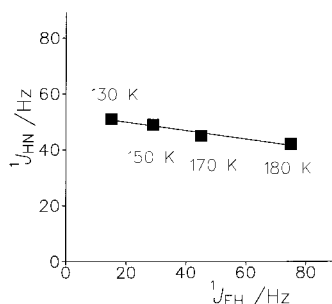


Figure 2. Experimental absolute values  $^1J_{\text{HN}}$  versus  $^1J_{\text{FH}}$  of the 1:1 complex between [<sup>15</sup>N]collidine and HF in the CDF<sub>3</sub>/CDF<sub>2</sub>Cl for different temperatures.

terms of a simple proton-transfer equilibrium between two forms  $^{19}\text{F}-^1\text{H}\cdots^{15}\text{N}$  ( $\equiv$  a)  $\rightleftharpoons$   $^{19}\text{F}^- \cdots ^1\text{H}-^{15}\text{N}^+$  ( $\equiv$  b) present in the mole fractions  $x_a$  and  $x_b$ , with each exhibiting a usual covalent bond and a hydrogen bond. In this case, the coupling constants observed represent averages for which the usual relations hold [Eqs. (1) and (2)], in which the term  $J_{\text{HX}}$  represents the intrinsic coupling constant between H and X (X = F, N) in form r (r = a, b). This equilibrium assumption

leads to the following linear relationship between the two constants [Eq. (3)] by the use of the relations  $K = x_b/x_a$  and  $x_a + x_b = 1$ . As the coupling constant associated to a usual covalent bond is substantially larger than for a usual hydrogen bond, Equation (3) approximates to Equation (4).

$$^1J_{\text{HN}} = x_a \ ^1J_{\text{HN}}^a + x_b \ ^1J_{\text{HN}}^b \quad (1)$$

$$^1J_{\text{FH}} = x_a \ ^1J_{\text{FH}}^a + x_b \ ^1J_{\text{FH}}^b \quad (2)$$

$$^1J_{\text{HN}} = \left\{ \frac{^1J_{\text{HN}}^a - ^1J_{\text{HN}}^b}{^1J_{\text{FH}}^a - ^1J_{\text{FH}}^b} \right\} ^1J_{\text{FH}} + \left\{ \frac{^1J_{\text{HN}}^b \ ^1J_{\text{FH}}^a - ^1J_{\text{HN}}^a \ ^1J_{\text{FH}}^b}{^1J_{\text{FH}}^a - ^1J_{\text{FH}}^b} \right\} \quad (3)$$

$$^1J_{\text{HN}} \approx - \left\{ \frac{^1J_{\text{HN}}^b}{^1J_{\text{FH}}^b} \right\} ^1J_{\text{FH}} + ^1J_{\text{HN}}^b \quad (4)$$

From the slope of  $-0.17$  of the calculated line in Figure 2 and the intercept, we obtain the intrinsic values  $^1J_{\text{HN}}^b \approx 54$  Hz and  $^1J_{\text{FH}}^a \approx 318$  Hz. We note that  $^1J_{\text{HN}}^b$  is significantly smaller than the typical value of  $^1J_{\text{HN}} \approx 90$  Hz for the protonated pyridine hydrogen bonded to Cl<sup>-</sup>[<sup>13c</sup>] and that  $^1J_{\text{FH}}^a$  is smaller than the value of 480 Hz reported for free hydrogen fluoride.[<sup>19</sup>] Therefore, the one-bond coupling constants do not corroborate a simple proton-transfer equilibrium between two tautomeric forms.

In the case of other samples with different HF/collidine (Col) concentrations ColHFHCol<sup>+</sup>, Col(HF)<sub>2</sub>, Col(HF)<sub>3</sub>, and FHF<sup>-</sup> complexes were also observed. In these complexes the two-bond coupling constants  $^2J_{\text{FN}}$  varied strongly between almost zero and the value for the 1:1 complex. The details of these results will be presented elsewhere.

## Discussion

**The reaction coordinate of proton transfer in a polar environment:** In order to interpret the new findings we firstly consider in Figure 3 typical hydrogen-bond properties as discussed in two recent papers.[<sup>13c, 14b</sup>] The configurations shown in Figure 3a represent various snapshots of the proton transfer from an acid AH to a base B in a hydrogen-bonded complex exhibiting different average nuclear positions. For simplicity we only consider a linear hydrogen bond. The potential curves for the proton motion (schematically) refer to fixed distances between heavy atoms  $q_2 = r_1 + r_2$  and a fixed environment, in which  $r_1$  and  $r_2$  represent the A $\cdots$ H and the H $\cdots$ B bond lengths. In the molecular complex A-H $\cdots$ B the proton is located on average closer to A, that is, the deviation  $q_1 = 1/2(r_1 - r_2)$  of the proton from the center of the hydrogen bridge is negative. When the acidity of AH or the basicity of B is increased the proton shifts towards the center of hydrogen bond. At the same time the distance between A and B ( $q_2$ ) goes through a minimum, leading to the strongly hydrogen-bonded complex A $\delta^- \cdots$ H $\cdots$ B $\delta^+$ . This complex exhibits a quasi-symmetric potential for the proton motion, and in the case of the collidine/HF complex a large scalar two-bond coupling constant between fluorine and nitrogen. After the proton has crossed the center of hydrogen bond  $q_2$  increases again in the zwitterionic complex A<sup>-</sup> $\cdots$ H-B<sup>+</sup>. The correlation between the  $q_2$  and  $q_1$  as indicated in Figure 3c was

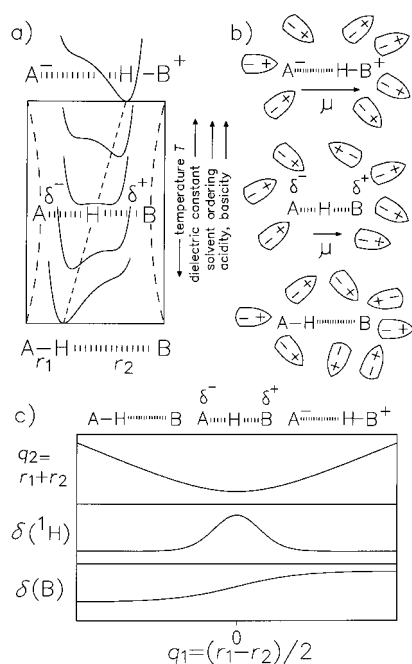


Figure 3. a) Average nuclear positions and proton potentials (schematically) of a 1:1 acid–base complex as a function of the proton-donating power of the acid AH, or the electric field created as a function of temperature at the complex site. b) Solvent-ordering-assisted proton transfer in a 1:1 acid–base complex. c) Correlation (schematically) proposed in ref. [14b] between the sum  $q_2 = r_1 + r_2$  (distance between the heavy atoms in the case of a linear hydrogen bond),  $^1\text{H}$  and heavy atom chemical shifts as a function of the deviation  $q_1 = \frac{1}{2}(r_1 - r_2)$  of the proton position from the center of the hydrogen bond.

reported recently<sup>[14b]</sup> and is based on NMR spectroscopic and theoretical results, as well as on a number of published neutron structures.<sup>[2c, 2d]</sup> Figure 3b also indicates schematically the behavior of the calculated  $^1\text{H}$  chemical shifts. A maximum low-field shift occurs approximately when the distance between A and B is at a minimum. At this point, the changes in chemical shift of the heavy atom nuclei are at a maximum.

The driving force for proton transfer is the electric field created by the electric dipoles of the individual solvent molecules at the solute site. This field is large if the dipoles are ordered and small if they are disordered. Because of the polarizability, the electric field induces a dipole moment in the acid–base complex that consists of two contributions. The electronic contribution is associated with charge transfer from the base to the acid and dominates in the molecular complex. The energy of the induced dipole is minimized by the contraction of the distance between A and B and the shift of the proton towards the center of the hydrogen-bond. The nuclear part, which is also called nuclear or vibrational polarizability, is particularly large and associated with changes of the nuclear geometry, leading to extremely broad IR absorption bands.<sup>[1]</sup> The nuclear polarizability dominates once the proton has crossed the center of the hydrogen-bond. Now, in the zwitterionic complex  $\text{A}^- \cdots \text{H} - \text{B}^+$ , in which charge separation has already occurred, the dipole moment is easily increased under the action of the solvent electric field, by an increase of the distance between the heavy atoms (A  $\cdots$  B) and

a decrease of the  $\text{H} \cdots \text{B}$  bond length, as indicated schematically in Figure 3b. These findings have recently been modeled by means of ab initio calculations of acid–base complexes in strong electric fields.<sup>[17]</sup>

**Chemical shifts of hydrogen-bonded acid–base complexes:** In Figure 4 we have plotted the temperature dependent  $^1\text{H}$  chemical shift changes of the collidine/HF complex reported in Figure 1, together with those of some other complexes studied previously.<sup>[13c]</sup> Qualitatively, the observed changes in

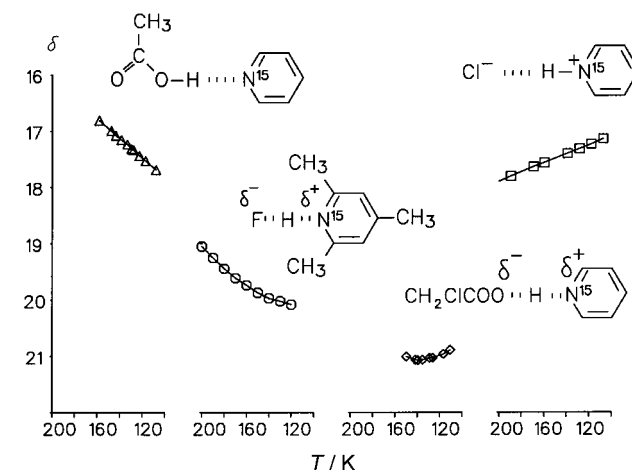


Figure 4. Temperature dependent  $^1\text{H}$  chemical shifts of hydrogen bonded protons in various 1:1 acid–pyridine (adapted from ref. [13c]) and HF/collidine complexes (this study).

$^1\text{H}$  chemical shift indicate that the distance between O and N in the molecular acetic acid/pyridine 1:1 complex contracts and the proton is displaced towards the center of the hydrogen bridge. The changes are further advanced in the collidine/HF complex. In the latter and in the chloroacetic/pyridine complex, maximum contraction and decreased proton shielding are observed. In the zwitterionic  $\text{HCl}/\text{pyridine}$ <sup>[13c]</sup> the distance between A and B increases again when the temperature is lowered.

**Scalar coupling constants of hydrogen-bonded acid–base complexes:** The finding of scalar spin–spin coupling between

all three atoms of the hydrogen bridge between [ $^{15}\text{N}$ ]collidine and HF embedded in a polar environment qualitatively corroborates the scenario shown in Figure 3. In this paper, no attempt was made to determine the signs of the coupling constants, and all values reported correspond to the absolute values. The dependence of the one-bond coupling constant  $^1J_{\text{HN}}$  on  $^1J_{\text{FH}}$  (Figure 2) could not be explained in terms of a simple tautomeric equilibrium. The values indicate a decrease of the  $\text{F} \cdots \text{H}$  bond order and the increase of the  $\text{H} \cdots \text{N}$  bond order at a constant  $\text{F} \cdots \text{N}$  bond order. The maximum value of  $^1J_{\text{HN}} \approx 54 \text{ Hz}$  at 112 K is substantially smaller than the value around 90 Hz for the pyridine/HCl complex.<sup>[13c]</sup> As a consequence, if it were possible to shift the proton further towards nitrogen leading to a further increase of  $^1J_{\text{HN}}$  we probably would find nonzero values of  $^1J_{\text{FH}}$  with an opposite sign, as found in the case of  $\text{F} \cdots \text{H} \cdots \text{F}^-$  hydrogen bonds.<sup>[20]</sup> Thus, in

the future the sign of the coupling will have to be considered as well as the absolute values. In conclusion, the one-bond coupling constants again indicate the formation of a quasi-symmetric complex  $A^{\delta-} \cdots H \cdots B^{\delta+}$  in collidine/HF and of a zwitterionic complex  $A^- \cdots H-B^+$  in the pyridine/HCl; increasing the temperature leads to a gradual transformation of  $A^{\delta-} \cdots H \cdots B^{\delta+}$  towards  $A-H \cdots B$ .<sup>[21]</sup>

The value of the two-bond coupling constant  ${}^2J_{\text{FN}} = 96$  Hz is larger than the largest known value of 52.6 Hz reported for 2-fluoropyridine,<sup>[22]</sup> and almost constant in the temperature range covered. This result indicates a through-space interaction of the lone pairs of fluorine and nitrogen leading to molecular orbitals delocalized over the whole complex, which exhibit s character both at fluorine and nitrogen. In the HF/collidine complex this interaction is apparently not affected by the small changes of the hydrogen-bridge structure with temperature. However, we note that preliminary observations in the case of the more asymmetric complexes  $\text{ColHFHCol}^+$ ,  $\text{Col}(\text{HF})_2$ ,  $\text{Col}(\text{HF})_3$  show that  ${}^2J_{\text{FN}}$  becomes smaller and eventually zero with increasing asymmetry of the  $\text{F} \cdots \text{H} \cdots \text{N}$  hydrogen bond. Therefore, the observation of substantial values of  ${}^2J_{\text{FN}}$  constitutes a novel criterion for the formation of strong, or low-barrier, or covalent hydrogen bonds. Through-space interactions between nitrogen and fluorine in ordinary organic compounds are well-known and can lead, for example, to coupling constants of about 23 Hz even if the two nuclei are separated over four covalent bonds, but are close in space.<sup>[23]</sup> In other words, the hydrogen bridge observed here is better regarded as a covalent three-center bond rather than as a purely electrostatic complex between two independent acid and base molecules. We note that the coupling of nitrogen to the distant fluorine is larger than to the close proton. This can perhaps be interpreted in the sense that the molecular orbitals exhibiting a large s character at fluorine and nitrogen exhibit a weaker s character at the proton. As large two-bond couplings between fluorine and nitrogen in the other complexes involving multiples of HF and collidine are smaller or absent, this through-space interaction of electron lone pairs across the hydrogen bond is possible only in the case of the formation of a very short hydrogen bond ( $A^{\delta-} \cdots H \cdots B^{\delta+}$ ) in the region of the minimum distance between A and B. This electronic aspect of low-barrier hydrogen bonds should be corroborated in the future by calculations of scalar coupling constants by means of novel computational methods.<sup>[24]</sup>

#### Thermodynamics of proton transfer in acid–base complexes:

The solvent reorientation around the solutes leads to a gain in energy, but also requires a decrease of the entropy. Therefore, the zwitterionic forms will be more stable at low temperature as depicted in the free energy diagrams of Figure 5. The conventional picture of proton transfer assumes that  $A^{\delta-} \cdots H \cdots B^{\delta+}$  is a transition state as illustrated in Figure 5a. By contrast, Figure 5b represents the case of a continuous temperature dependent distribution of stationary states exhibiting various geometries. Here, the quasi-symmetric complex dominates at an intermediate transition temperature that is high for the zwitterionic pyridine/HCl complex and very low for the molecular complexes. This transition temper-

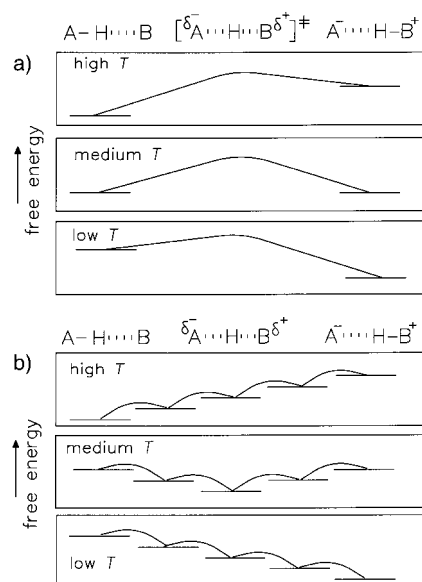


Figure 5. Temperature-dependent free-energy reaction profiles of a conventional proton transfer in a 1:1 acid–base complex. a) The case in which  $A^{\delta-} \cdots H \cdots B^{\delta+}$  corresponds to a transition state. b) The case in which  $A^{\delta-} \cdots H \cdots B^{\delta+}$  corresponds to a stationary state.

ature is only achieved experimentally in the case of the collidine/HF and the pyridine/chloroacetic acid complexes.

#### Implications for acid–base catalysis in aprotic, but polar, environments:

During acid–base catalysis in aprotic, but not necessarily apolar, environments the problem arises that the  $pK_a$  value of the protonated base measured for water as solvent may not match the value of the interacting weak acid. Conventionally, the situation would have been characterized by the high temperature case of Figure 5a in which  $A^{\delta-} \cdots H \cdots B^{\delta+}$  corresponds to a transition state that does not particularly contribute to the catalytic activity. If we accept, however, that due to a local electric field  $A^{\delta-} \cdots H \cdots B^{\delta+}$  is a stationary state as indicated in Figure 5b and is also the active nucleophile of the reaction instead of free  $A^-$  or the ion pair, it becomes clear that the base B may have catalytic activity by a low-barrier hydrogen-bond formation to AH in spite of a  $pK_a$  mismatch. Thus, a full proton transfer to B is avoided, which would require much more free energy. This idea might also apply to enzyme reactions whenever the catalytic site is not completely surrounded by bulk water.

Naturally, the above model systems refer to a single hydrogen bond between an acid and a base. The situation will be more complicated in cooperative hydrogen bonds requiring the study of larger model systems. This can be done in the future also by low-temperature NMR spectroscopy by use of the technique of secondary isotope effects on chemical shifts.<sup>[13b]</sup> Preliminary experiments showed that a linear neutral complex  $A-H \cdots A-H \cdots B$  gradually turned into the complex  $A-H \cdots A^- \cdots H-B^+$  when the acidity of AH was increased. By contrast, in the case of a negatively charged complex  $A-H \cdots B-H \cdots X^-$ , which constitutes a true charge relay chain, evidence for the formation of  $A^{\delta-} \cdots H \cdots B^{\delta-} \cdots H \cdots X^{\delta-}$  was obtained.<sup>[5]</sup>

## Conclusions

By observing all nuclear scalar coupling constants of a hydrogen bridge we have obtained evidence that a molecular acid–base complex  $A-H\cdots B$ , stable at high temperature or at low dielectric constants of the solvent, gradually transforms into the stable species  $A^{\delta-}\cdots H\cdots B^{\delta+}$  and eventually into the zwitterionic form  $A^{-}\cdots H-B^{+}$  when the temperature is decreased and the dielectric constant of the solvent increased. Thus, an increasing polarity of the environment does not destabilize neutral low-barrier hydrogen bonds, but produces them. Enzymic acid–base catalysis is then possible because the formation of the low-barrier hydrogen bonds means that energetically unfavored complete transfers are avoided.

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