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Observation and characterization by ^{15}N CPMAS NMR of a double proton transfer in cyclic dimers of $^{15}N,^{15}N'$-di-(4-bromophenyl)-formamidine in the solid state

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Abstract

Using dynamic ^{15}N CPMAS NMR spectroscopy a novel double proton transfer was detected in the cyclic hydrogen bonded dimers of polycrystalline $^{15}N,^{15}N'$-di-(4-bromophenyl)-formamidine. Rate constants of this process, which is degenerate within the margin of error, were obtained by lineshape ($k_{12} = 10^{6.6}$ exp(-9.7 kJ mol$^{-1}/RT$) s^{-1}, 110 K $\leq T \leq$ 142 K) and ^{15}N T_1 data analysis (minimum at 324 K and 9.12 MHz, $^1H-^{15}N$ distance $r_{HN} = 1.11$ Å, $k_{12} = 10^{10.9}$ $\times$exp(-21.5 kJ mol$^{-1}/RT$) s^{-1}, 240 K $\leq T \leq$ 370 K). The non-Arrhenius behavior observed indicates proton tunneling at low temperatures.

1. Introduction

Whereas the dynamics of double proton transfer in cyclic dimers of carboxylic acids [1–4] (Fig. 1a), pyrazoles [5,6], and excited azaindoles [7–10] (Fig. 1b) are a matter of intensive experimental and theoretical study, little is known about the tautomerism of the intermediate amidines (Fig. 1c). This class of molecules exhibits antiviral, antibacterial and antihypertensive activity [11] depending on the chemical structure, conformation and hydrogen bonding pattern. Information on these properties is therefore highly desirable. In this Letter we present evidence by NMR of a tautomerism of an amidine in the solid state.

Experimental evidence for the tautomerism of symmetric N,N'-diarylamidines dissolved in organic liquids was obtained by Borisov et al. [12] by NMR spectroscopy. Additionally, it was shown that these molecules are also subject to a conformational s-cis/s-trans isomerism [12,13]. The thermodynamics of this isomerism and of the cyclic dimer formation of N,N'-diarylformamidines dissolved in tetrahydrofuran have been studied by dynamic liquid state NMR spectroscopy [14–16]; moreover, rate constants of the double proton transfer within the cyclic dimers (Fig. 1c) could be measured as a function of temperature including the kinetic HH/HD/DD isotope effects [16]. These results indicated a hydrogen bond contraction assisted proton tunneling process where the difference between a concerted and stepwise proton transfer is minimal. Two ab initio studies of the parent formamidine dimer showed that the energetic difference between these two types of tran-

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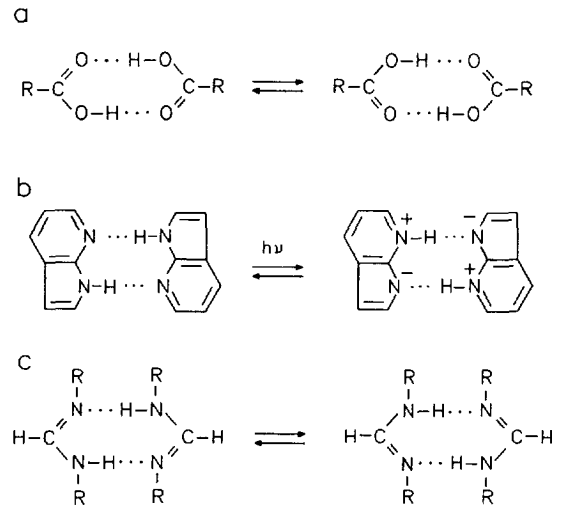

Fig. 1. Double proton transfer in cyclic dimers of carboxylic acids (a), azaindoles (b) and amidines (c).

sition states is not particularly large [17,18]. On the other hand, both the theoretical prediction as well as the interpretation of experimental kinetic hydrogen/deuterium isotope effects of proton transfer reactions is still difficult as these effects are influenced by zero-point energy changes along the reaction pathways as well as by proton tunneling [19]. Therefore, the reactions depicted in Fig. 1 constitute model examples for testing more elaborate quantum-mechanical dynamic theories, as previously shown in the case of carboxylic acid dimers [3,4]. However, such theories require simple and well-defined proton transfers and kinetic data over a wide temperature range which are difficult to obtain for liquid solutions and are furthermore complicated by conformational exchange, hydrogen bond equilibria and solvent effects.

Therefore, we thought it would be interesting to search for double proton transfers in solid diarylamidines in order to evaluate chemical differences between the cases of carboxylic acids, pyrazoles and azaindoles. This search was facilitated by a recent publication on several X-ray crystallographic structures of diarylamidines showing that this class of molecules forms cyclic dimers in the solid state [20–22], and is in agreement with the liquid state results [14–16]. We employed high resolution solid state ^{15}N CPMAS NMR spectroscopy (CP ≡ cross polarization, MAS ≡ magic angle spinning) of ^{15}N enriched compounds, a method which has been shown to be useful in obtaining rate constants of solid state proton transfers between nitrogen, by lineshape analysis [5,6,28] on a millisecond timescale. Recently, even micro- to nanosecond solid state proton transfers could be followed using this method, i.e. by analyzing ^{15}N longitudinal relaxation times T_1 obtained under MAS conditions [28].

In this Letter we report the results of a dynamic ^{15}N CPMAS NMR study of ^{15}N enriched polycrystalline N,N′-di-(4-bromophenyl)-formamidine (DBrFA). The X-ray crystal structure of DBrFA according to Ref. [20] is illustrated in Fig. 2a, where the hydrogen bond proton positions were obtained in this study by NMR. DBrFA constitutes the first example of an amidine exhibiting a fast, solid state double proton transfer according to Fig. 1c. Within the margin of error, the process is degenerate. Rate constants of the tautomerism are reported here over a wide temperature range providing evidence of a non-Arrhenius behavior as expected for thermally assisted proton tunneling.

2. Experimental

^{15}N enriched DBrFA was synthesized according to the method of Claisen [29] from triethylorthoformate and 95% enriched 4-bromoaniline-^{15}N. The latter was obtained using methods described for the unlabeled material [30,31]. The ^{15}N CPMAS spectra were recorded at 9.12 MHz (2.1 T cryomagnet) with a Bruker CXP 100 NMR spectrometer equipped with a standard 7 mm Doty probehead. For the measurement of the ^{15}N longitudinal relaxation times T_1 in connection with the CP scheme, a pulse sequence described by Torchia [32] was employed. Due to phase cycling of the first proton 90° pulse and of the receiver phase, the equilibrium magnetization is zero in this experiment, which is contrary to the most frequently applied inversion–recovery pulse sequence where equilibrium magnetization approaches maximum intensity. Between 500 and 2500 scans were accumulated on average, with a contact time for cross polarization of between 1.5 and 5.0 ms, and a repetition time of 1 to 3 s. Low temperature

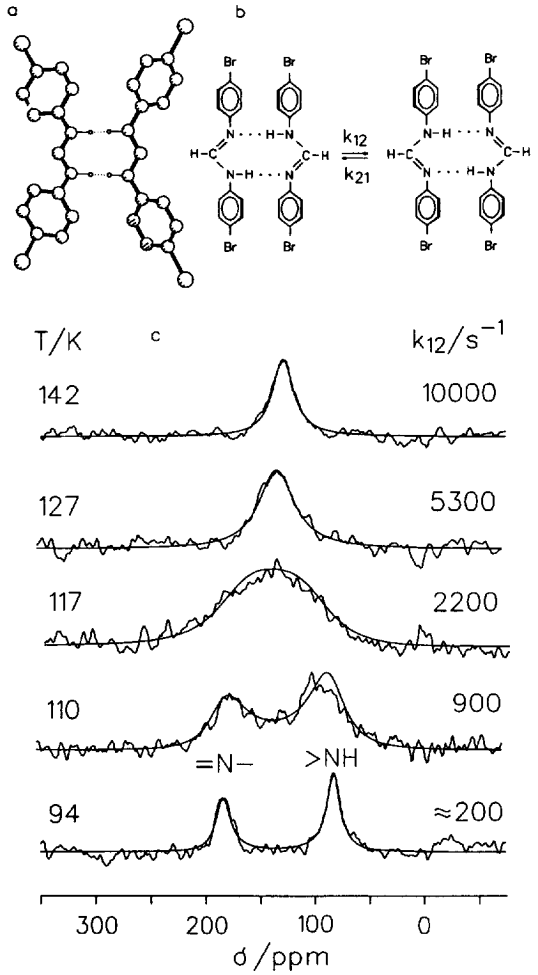

Fig. 2. (a) Structure of cyclic dimers N,N′-di-(4-bromophenyl)-formamidine (DBrFA) in the solid state according to Ref. [20]; only the positions of the heavy atoms are shown besides the positions of the disordered hydrogen bond protons established in this study by NMR; (b) The tautomerism of cyclic dimers of DBRFA; (c) Superposed experimental and calculated variable temperature ^{15}N CPMAS NMR spectra (9.12 MHz) of 95% ^{15}N enriched polycrystalline DBrFA.

measurements were carried out by passing nitrogen gas through a home built heat exchanger [33] immersed in liquid nitrogen, thus allowing temperatures as low as 90 K to be achieved, maintaining the spinning speeds between 2 and 2.5 kHz which were large enough for obtaining essentially rotational side band-free spectra. Chemical shifts were referenced to external solid $^{15}NH_4Cl$.

3. Results

The superposed experimental and calculated variable temperature ^{15}N CPMAS NMR spectra of polycrystalline DBrFA are depicted in Fig. 2. At room temperature, only one sharp singlet is observed at 134 ppm indicating that all nitrogen sites are equivalent. When the sample is cooled, the line broadens only below 140 K and eventually splits into two single lines at 83 and 185 ppm below the coalescence point of about 115 K. The high field line arises from the protonated and the low-field line from the non-protonated nitrogen atoms; the small line distortions arise from different cross-polarization times of the two nitrogen sites.

It is well established [23–28], that in the case of non-degenerate solid state proton transfer between nitrogen atoms, two ^{15}N lines are observed in the fast exchange regime with a line splitting given by $\delta\nu = \Delta\nu(1 - K_{12})/(1 + K_{12})$, where $\Delta\nu$ represents the chemical shift difference in the slow exchange regime, $K_{12} = k_{12}/k_{21}$ the equilibrium constant of the proton transfer. k_{12} and k_{21} are the corresponding forward and backward rate constants. As we do not find a splitting in the case of DBrFA, $\delta\nu$ must be smaller than the linewidth W_0 in the absence of exchange. With $W_0 \approx 4$ ppm above 200 K and $\Delta\nu \approx 102$ ppm we estimate therefore values of K_{12} between 0.9 and 1.1, i.e. a degenerate process within the margin of error.

The lineshape analysis was done as described previously [23–28] in terms of two-site exchange theory; K_{12} was set to 1 over the whole temperature range, W_0 was extrapolated from the linewidth in the slow and fast exchange regime as usual and the rate constants $k_{12} = k_{21}$ were obtained by simulation of the spectra as indicated in Fig. 2b. The rate constants obtained are assembled in Table 1 and their temperature dependence can be expressed by

$$k_{12} = 10^{6.6} \exp\left(-9.7\,\mathrm{kJ\ mol^{-1}}/RT\right)\ \mathrm{s^{-1}},$$
$$110\,\mathrm{K} \le T \le 142\,\mathrm{K}. \qquad (1)$$

Above 142 K the rate constants could no longer be obtained by line-shape analysis as the exchange broadening contribution to the signal line widths became negligibly small. However, rate constants could be obtained in the micro to nanosecond time

Table 1
Rate constants k_{12} of double proton transfer in cyclic dimers of polycrystalline DBrFA as a function of temperature T obtained by ^{15}N CPMAS NMR lineshape analysis and analysis of the ^{15}N-T_1 relaxation times

T (K)	^{15}N-T_1 (s)	k_{12} (s^{-1})	T (K)	^{15}N-T_1 (s)	k_{12} (s^{-1})
110	–	900	260	1.43	4.84×10^6
117	–	2200	264	1.35	5.15×10^6
122	–	4200	272	1.04	6.88×10^6
127	–	7300	296	0.56	1.57×10^7
142	–	10300	305	0.52	1.75×10^7
240	3.85	1.75×10^6	321	0.49	2.14×10^7
240	2.89	2.35×10^6	326	0.47	2.39×10^7
250	2.72	2.50×10^6	336	0.48	4.15×10^7
251	2.78	2.44×10^6	356	0.59	6.65×10^7
252	3.01	2.25×10^6	370	0.62	7.30×10^7

scale by analysis of the longitudinal ^{15}N relaxation times T_1^{mas} obtained under magic angle spinning conditions. An example of such an experiment is depicted in Fig. 3a. As described previously [28], the proton transfer leads to the modulation of the dipolar $^1H-^{15}N$ interaction providing a source of longitudinal relaxation. To good approximation, T_1^{mas} is equal to the isotropic values T_1, when the proton jumps rapidly and frequently within one rotor cycle of the magic angle spinning process. Therefore, we can omit the superscript. The relation between T_1, the rate and equilibrium constants k_{12} and K_{12} and the $^1H-^{15}N$ distance r_{HN} has been described [28]. A plot of the data obtained at a magnetic field of 2.1 T in the temperature region between 240 and 370 K are depicted in Fig. 3b. A T_1 minimum of 0.47 s was obtained at 324 K. In a first stage an Arrhenius expression was used to calculate the solid line in Fig. 3b by non-linear least squares fitting, varying the energy of activation, the pre-exponential factor and the distance r_{HN}. We obtained a value of $r_{HN} = 1.11$ Å. This value was then applied in the next stage to convert the ^{15}N-T_1 values to rate constants k_{12}, in a similar way as described previously [28]. The constants are assembled in Table 1; their temperature dependence can be expressed by

$$k_{12} = 10^{10.9}\exp(-21.5\,\text{kJ mol}^{-1}/RT)\ \text{s}^{-1},$$
$$240\,\text{K} \le T \le 370\,\text{K}. \qquad (2)$$

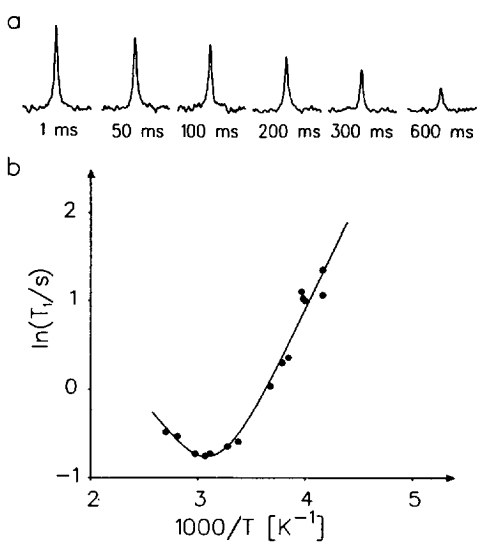

Fig. 3. (a) Measurement of the longitudinal ^{15}N relaxation time T_1 at 336 K of the sample of Fig. 2b at 9.12 MHz rotating at the magic angle. (b) Plot of ln T_1 vs. inverse temperature. The solid line was calculated as described in the text.

4. Discussion

Using variable temperature solid state high resolution ^{15}N CPMAS NMR we found a double proton transfer in cyclic dimers of ^{15}N, $^{15}N'$-di-(4-bromophenyl)formamidine DBrFA in the solid state which is degenerate within the margin of the experimental error. Rate constants k_{12} were obtained on a milli- to nanosecond timescale by ^{15}N lineshape analysis and by analysis of the ^{15}N longitudinal relaxation times T_1 obtained under magic angle spinning conditions. The T_1 analysis in terms of a dipolar relaxation mechanism caused by the proton jumps also provided the cubic average distance $r_{HN} = 1.11$ Å used to incorporate the positions of the dynamically disordered hydrogen bond protons into the molecular skeleton derived by X-ray crystallography [20] which cannot easily locate protons.

The resulting complete Arrhenius diagram is depicted in Fig. 4. For comparison the Arrhenius curve of the related tautomerism of $^{15}N,^{15}N'$-di-(4-fluorophenyl)formamidine (DFFA) established previously for the cyclic dimer dissolved in tetrahydrofuran [16] is included as a dotted line.

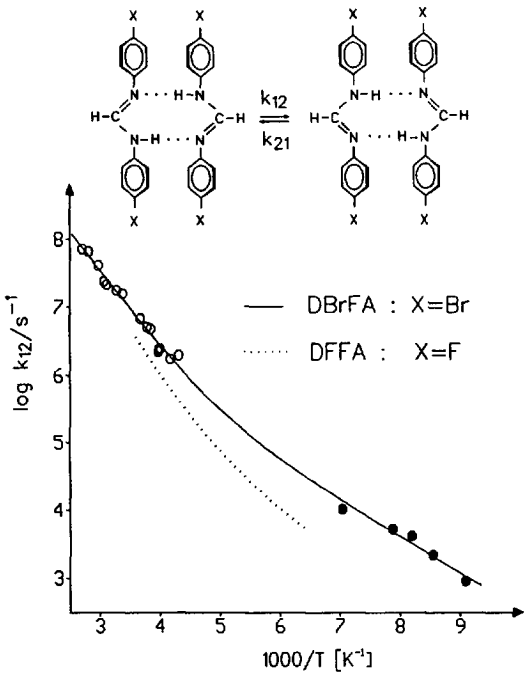

Fig. 4. Arrhenius diagram of the double proton transfer in cyclic dimers of polycrystalline DBrFA. The open circles represent data obtained by ^{15}N CPMAS NMR lineshape analysis, the closed circles by analysis of the ^{15}N longitudinal relaxation times T_1. For comparison the kinetic data obtained in Ref. [16] for the double proton transfer in cyclic dimers of N,N'-di-(4-fluorophenyl)formamidine (DFFA) dissolved in tetrahydrofuran are included as dotted lines.

The rate constants of both systems are similar which confirms the previous interpretation. Moreover, the former proposition of a non-Arrhenius behavior is further corroborated by the larger temperature range where rate constants were observed.

In order to obtain further information on this phenomenon we are currently measuring the kinetic HH/HD/DD isotope effects of the tautomerism of DBrFA. The results of this study will be presented in a forthcoming paper.

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