Tautomerism of 4-hydroxyterpyridine in the solid, solution and gas phases: an X-ray, FT-IR and NMR study

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The keto–enol equilibrium between 2,6-bis(2′-pyridyl)-4-pyridone **1b** and 2,6-bis(2′-pyridyl)-4-hydroxypyridine **1a** was evaluated using infrared spectroscopy, variable temperature ^{1}H and ^{13}C NMR spectroscopy and X-ray crystallography. These studies show that the less polar hydroxy tautomer **1a** is the predominant species in the gas phase. The solution-state studies show the more polar keto form **1b** to be predominant but not exclusive, and the ratio of tautomers depends on the polarity and hydrogen-bonding ability of the solvent as well as temperature. In the solid-state both species are present in a 1 : 1 ratio and form a dimeric structure held together by a strong C=O · · · H–O hydrogen bond between the tautomers.

Introduction

Heterocyclic compounds, which can exist as a mixture of rapidly equilibrating tautomers, play interesting roles in both chemical and biochemical processes.[1–3] Tautomerism can provide a rationale for the structure–function relationships in nucleotides, mechanism of enzyme catalysis and substrate–receptor interactions. The ability to accurately predict the position of the tautomeric equilibrium in such compounds is critical in order to create useful models for biochemical transformations, as well as when designing solution and solid-state supramolecular structures.

The factors that affect the position of tautomeric equilibria have been the subject of many studies. The interconversion between the keto and enol forms of 4-hydroxypyridine has received considerable attention.[4–11] In the gas phase, where solvent-assisted stabilization is absent, and in non-polar solvents such as cyclohexane, the enol isomer is the predominant species.[10,11] It has also been shown that the keto form exists exclusively in polar solvents such as dimethyl sulfoxide[5,10,11] as well as in the solid-state[12–18] where efficient solvation and intermolecular hydrogen bonding are key stabilizing factors, respectively.

Previous studies have also illustrated that incorporating secondary structural features into heterocycles can upset the position of the hydroxypyridine–pyridone equilibrium. For example, the population of the less favorable hydroxy form is increased through: (1) intermolecular[19,20] and intramolecular[21–28] hydrogen-bonding of the hydroxy hydrogen and an appropriately placed hydrogen bond acceptor, or (2) a reduction in the proton affinity of the pyridine nitrogen atom through the incorporation of electron withdrawing groups and consequently a reduction in the efficacy of the nitrogen in acting as a hydrogen bonding acceptor[29–32] (Chart 1). These studies have successfully demonstrated the power of substituents and hydrogen bonding to govern the position of the tautomeric equilibrium.

Numerous studies have taken advantage of 4-hydroxyterpyridine **1** as a ligand to prepare coordination compounds.[33–37] It appears that the choice of nomenclature is at the discretion of the authors as the terpyridine backbone appears in the literature in both its keto and enol forms. There has not been a study to date that rigorously investigates the influence of the environment on the tautomeric equilibrium in this interesting molecule. In this context, the effects of external species and the basic nitrogens positioned by the terminal pyridine rings to effectively stabilize electrostatic charge build-up must both be addressed. Here we study the question of how the populations of terpyridines **1a** and **1b** vary when the environment is changed from the solid-, to the solution-, and finally to the gas-state. The use of X-ray crystallographic analysis, infrared spectroscopy, ^{13}C CPMAS and ^{1}H NMR spectroscopy to investigate the equilibrium is reported and discussed. The influence of temperature on the tautomeric population is also described.

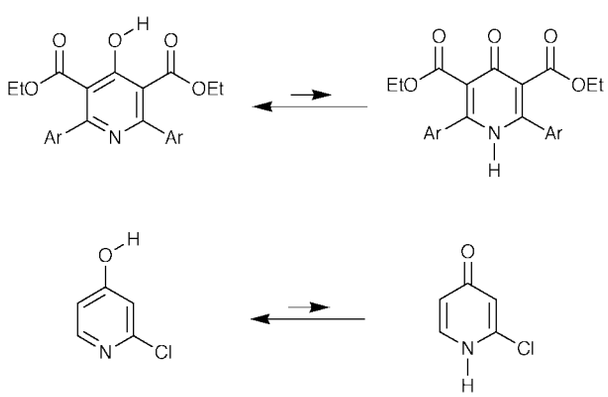
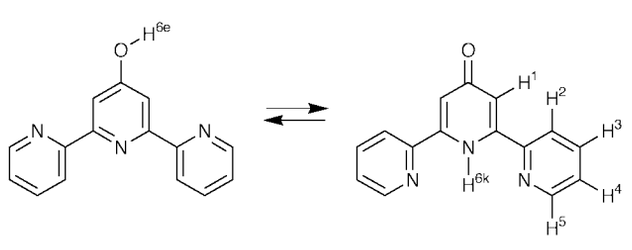


Chart 1



1a **1b**

Experimental

All solvents (Caledon) were distilled prior to use. Solvents for NMR analysis (Cambridge Isotope Laboratories) were used as received. ^{1}H NMR characterizations were performed on a Varian Inova-300 instrument, working at 299.96 MHz.

Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane using the residual solvent peak as a reference standard. Coupling constants (J) are reported in Hertz. FT-IR measurements were performed using a Nicolet Magna-IR 750 (solution phase studies), Nicolet-Plan IR Microscope (solid-state studies) and Hewlett-Packard GC–IR fitted with an HP1 column (25 m × 0.32 mm id × 0.52 μ film) for the gas phase studies.

Preparation of 2,6-bis(2′-pyridyl)-4-pyridone (1), 2,6-bis(2′-pyridyl)-4-methoxypyridine (2) and 2,6-bis(4′-pyridyl)-4-pyridone (3)

Parent compound **1** was prepared in two steps by condensation of ethyl picolinate and acetone under basic conditions.[36] The intermediate 1,5-bis(2′-pyridyl)pentane-1,3,5-trione was cyclized in the presence of excess ammonium acetate to afford multi-gram quantities of **1** in high yield.[37] The corresponding methoxy derivative **2** was prepared from **1** by treatment with iodomethane in acetone under basic conditions.[38] Isomer **3** was prepared in an analogous fashion to **1** from ethyl isonicotinate. The structures of **1**, **2** and **3** were verified by ^{1}H and ^{13}C NMR spectroscopy, infrared spectroscopy and electrospray mass spectrometry (ES-MS).

^{1}H and ^{13}C NMR spectroscopy

^{13}C CP MAS NMR spectra were obtained at 25 °C on a Bruker AMR300 spectrometer. For this purpose a 7-mm Bruker DAB 7 probehead which achieves rotation frequencies up to 5 kHz was used. The standard CP pulse sequence was applied with a 6.8 μs ^{1}H-90° pulse width, 2 ms contact pulses, 2 s repetition time and a spectrum width of 35 kHz. Chemical shifts are reported with respect to the spectrometer frequency, which was calibrated by the adamantane signal at 38.56 ppm.

For ^{1}H NMR dilution experiments, a concentrated solution of **1** (1 molar) was prepared in the appropriate solvent. A 500 μL aliquot of this solution was transferred to an NMR tube and subsequently diluted with the appropriate pure deuterated solvent. The procedure was repeated to sub-millimolar concentrations. Spectra were recorded with increasing acquisition times for diluted samples. ^{1}H NMR variable temperature (VT) spectra were obtained from 25 to −80 °C on a Bruker AM400 spectrometer, working at 400.13 MHz. Temperatures were calibrated with a copper/constantan thermocouple and are accurate to ±1 °C.

X-Ray analysis †

The crystal structure was solved using direct methods (SHELXL-86) and refined by full-matrix least squares on F^2 (SHELXL-93).[39] The hydrogen atoms attached to O(1A) and N(1B) were located from a difference Fourier map, then refined in idealized positions (H(1OA) as a hydroxy proton hydrogen-bound to O(1B); H(1NB) as attached to an sp^2-hybridized nitrogen atom); all other hydrogens were generated in idealized positions according to the sp^2- or sp^3-hybridized geometries of their attached carbon atoms. V (Å^3) = 2894.1(3), Z = 4, final $R_1(F)$ = 0.0595 (for 2748 data with $F_o^2 \geq 2\sigma(F_o^2)$), $wR_2(F^2)$ = 0.1415 (on all data), and S = 1.059 for 379 parameters varied. The largest difference peak and hole in the final difference Fourier map had intensities of 0.405 and −0.469 e Å^{-3}, respectively.

Results and discussion

X-Ray crystallographic analysis

Single crystals of **1** suitable for X-ray crystallographic analysis were obtained by slow evaporation of a chloroform solution. The crystal structure shows that **1** exists as a dimer comprised of an equimolar mixture of tautomers (Fig. 1). This mixed-dimer is held together by a strong intermolecular hydrogen bond (OH · · · O distance of 1.702 Å) between the hydroxy hydrogen of one tautomer and the carbonyl oxygen of the other [O(1A)–H(1OA) · · · O(1B)]. The mixed-dimer we report here is analogous to one previously observed by Bradshaw and Izatt.[20] These authors describe a 4-pyridone system in which a crown ether appendage steers the nitrogen atom of aniline into a position where it can act as a strong hydrogen bond acceptor to the N–H hydrogen atom of the pyridone heterocycle. In this way, the 4-pyridone is forced to exist as the keto isomer. The authors report the presence of one equivalent of the 4-hydroxypyridine isomer, which acts as a hydrogen bond donor in the same way as we describe for this system.

The identity of each tautomer was unambiguously determined by the location of the N–H and O–H hydrogen atoms in difference Fourier calculations and by C–N and C–O bond lengths (Table 1). One terpyridine species displays nitrogen-to-

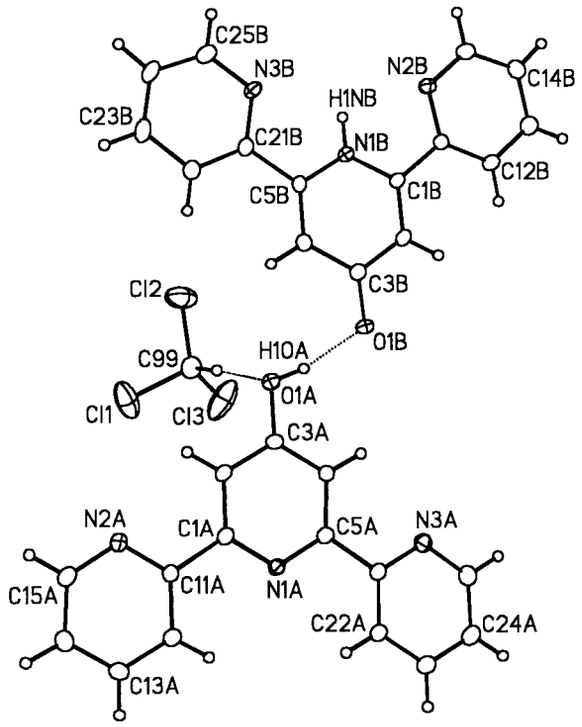


Fig. 1 View of the mixed-dimer illustrating intermolecular C=O · · · H–O and Cl_3CH · · · O–H hydrogen bonds between tautomers, as well as with the chloroform molecule (shown as dashed lines).

Table 1 Selected interatomic distances (Å) from the X-ray structure of **1**

Enol tautomer **1a**		Keto tautomer **1b**	
Bond	Distance/Å	Bond	Distance/Å
O1A–C3A	1.351(4)	O1B–C3B	1.279(4)
N1A–C1A	1.349(4)	N1B–C1B	1.362(4)
N1A–C5A	1.342(5)	N1B–C5B	1.357(5)
C1A–C2A	1.393(5)	C1B–C2B	1.356(5)
C2A–C3A	1.376(5)	C2B–C3B	1.420(5)
C3A–C4A	1.391(5)	C3B–C4B	1.432(5)
C4A–C5A	1.387(5)	C4B–C5B	1.363(5)
N2A–C11A	1.335(5)	N2B–C11B	1.341(5)
N2A–C15A	1.337(5)	N2B–C15B	1.337(5)
C11A–C12A	1.393(5)	C11B–C12B	1.381(5)
C12A–C13A	1.379(5)	C12B–C13B	1.375(5)
C13A–C14A	1.360(5)	C13B–C14B	1.375(5)
C14A–C15A	1.378(5)	C14B–C15B	1.380(5)

† CCDC reference number 188/189. See http://www.rsc.org/suppdata/p2/1999/2789 for crystallographic files in .cif format.

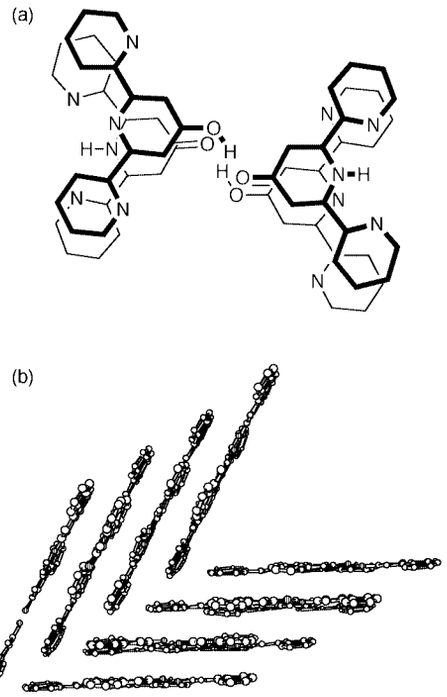


Fig. 2 Cross section of the crystal packing diagram of the dimeric species **1** illustrating (a) the offset π–π stacked parallel layers, and (b) the herringbone arrangement of the parallel layers.

carbon bond lengths of 1.349(4) and 1.342(5) Å in the central ring [N(1A)–C(1A) and N(1A)–C(5A)] which are comparable to those found in standard aromatic pyridines (1.349 Å) and an oxygen-to-carbon bond length of 1.351(5) Å [O(1A)–C(3A)] which is consistent with a C–O single bond.[40] This species was assigned as the hydroxy tautomer **1a**. In this species, the *trans–trans* orientation of the three nitrogen atoms with respect to each other eliminates any repulsive N···N lone pair interactions that would be present in the *cis–cis* conformation as well as maximizes weak electrostatic interactions between N(3A)···H(C4A) and N(2A)···H(C2A). This conformational preference plays a critical role in the ^{1}H NMR analysis as will be described in later sections. The second component of the mixed-dimer displays a significantly shorter oxygen-to-carbon bond length (1.279(4) Å) [O(1B)–C(3B)] which is comparable to those found in carbonyl C=O double bonds.[40] The nitrogen-to-carbon bond lengths in the central ring of this species [N(1B)–C(1B) and N(1B)–C(5B)] are slightly longer than those in isomer **1a** (1.362(4) and 1.357(5) Å) showing their increased single bond character. This species was assigned as the keto tautomer **1b**. In this case, the cisoid orientation of the three nitrogen atoms results in strong intramolecular NH···N hydrogen bonds (N(2B) and N(3B)···H(1NB) distances of 2.196 Å).

There also exists one chloroform molecule for each terpyridine mixed-dimer in the crystal structure. The proton of this solvent molecule (H99) is acting as a hydrogen bond donor to the lone-pair electrons of the hydroxy group of the enol tautomer **1a**. The fact that the chloroform proton is hydrogen bonded to the hydroxy oxygen (O1A) of **1a** and not the more basic C=O oxygen of the keto-isomer **1b** (O1B) appears to be counter-intuitive. This phenomenon is not completely unreasonable, however, as it is expected that the hydroxy oxygen atom will exhibit an increase in basicity as it forms an intramolecular hydrogen bond to the keto tautomer.

The packing diagram of **1** shows that the mixed-dimers arrange into parallel sheets stacked in such a manner as to maximize favorable offset π–π stacking interactions (Fig. 2a). The shortest distance between the π-stacked planes is 3.404 Å. These parallel sheets arrange in a "herringbone" fashion that extends throughout the crystal (Fig 2b). There are channels that run within the planes at the junction of each stacked sheet in the "herringbone" motif (not shown). It is within these channels that the ordered solvent molecules reside. This sheds light on the preference for the hydrogen atom of the chloroform to interact with the hydroxy oxygen of **1a**. The lone pair electrons of the oxygen in **1b** lie in the plane defined by the mixed-dimers and are thus less accessible than those for **1a** which point into the channels.

Table 2 ^{13}C CPMAS DPD NMR data (δ) for terpyridine **1** [a]

δ C3A	δ C3B	δ C1, C5 (A, B)	δ C11, C21 (A, B)
167.77	180.91	155.25	146.90

[a] Numbering scheme corresponds to that described in the crystal structure (Fig. 1).

Solid-state analysis using ^{13}C NMR spectroscopy

The solid-state ^{13}C CPMAS NMR results are consistent with the X-ray crystallographic analysis. In the ^{13}C NMR spectrum, there are nine signals, seven of which are broadened due to overlapping resonances of the two tautomers as well as partially unaveraged dipolar interactions between adjacent ^{13}C and ^{14}N atoms.[41] The two furthest downfield signals (δ 180.91 and 167.77) were assigned as the carbonyl C=O (C3B) and the phenolic C–OH (C3A) carbons respectively. A dipolar dephasing (DPD) ^{13}C NMR experiment, which suppresses all signals except those that correspond to carbonyl and quaternary carbons, corroborates this assignment. As anticipated, this spectrum shows, in addition to the two downfield signals identified above, signals at δ 155.25 and 146.90 (Table 2). Integration shows the relative signal intensities of the four signals to be 1 : 1 : 4 : 4 which were assigned as C(3B), C(3A), C(1A, 5A) and C(1B, 5B), C(21A, 11A) and C(21B, 11B) respectively (see Fig. 1 for atom labeling scheme). The resonance at δ 155.25 corresponds to the C1 and C5-carbon atoms and is identical for both tautomeric forms of **1**. This also holds true for the signal at δ 146.90, which represents carbons C11 and C21. This highlights the efficacy of ^{13}C CPMAS NMR as a diagnostic technique for quantifying solid-state tautomeric populations. This technique is utilitarian in the absence of a crystal suitable for X-ray analysis.[42,43]

Infrared spectroscopic analysis

The gas phase FT-IR spectrum of **1** was obtained using coupled GC/FT-IR analysis. Only one major molecular species eluted as evidenced by a single sharp peak in the GC trace. The FT-IR spectrum of this species exhibits a sharp absorbance at $\tilde{\nu}$ 3640, characteristic of an "isolated" hydroxy stretch (Fig. 3a).[44] The spectrum also shows a very weak C=O stretching band at 1635 cm^{-1}. These observations suggest that the hydroxy tautomer **1a** may exist almost exclusively in the gas phase. It is not certain whether the predominance of **1a** using this technique can be attributed to a preference for the less polar enol tautomer.[45] It may also be an artifact of the column stationary phase, which may retain **1b**, or effect the preferential stabilization of **1a**.

The solution IR spectrum of **1** in $CHCl_3$ (Fig. 3b) and CH_3OH (not shown) reveals the presence of an N–H stretch at $\tilde{\nu}$ 3310 cm^{-1} and a C=O stretch at $\tilde{\nu}$ 1630 cm^{-1}. These absorbances, combined with the absence of an O–H stretch indicate the presence of only the keto tautomer **1b** in these solvents. The solution IR spectrum of **1** in CH_2Cl_2 at 25 °C is similar to that of $CHCl_3$; however, subsequent variable temperature ^{1}H NMR studies discussed in the following section argue the existence of the hydroxy tautomer as well. These results are in good agreement with previous experimental studies done on the 4-hydroxypyridine–pyridone system, where the tautomeric

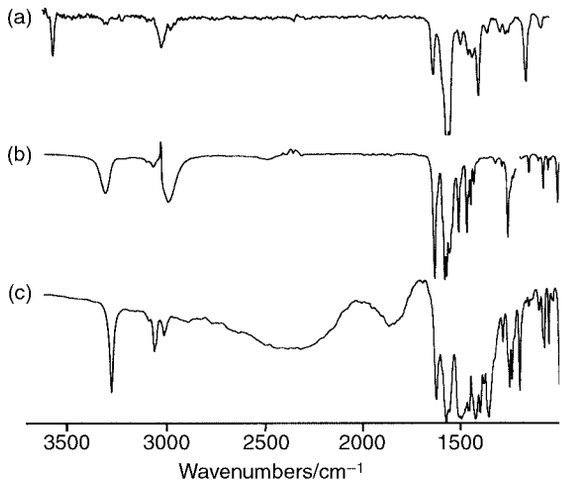


Fig. 3 FT-IR spectrum of terpyridine **1** in (a) the vapor phase (190 °C), (b) $CHCl_3$ solution at 25 °C, (c) the solid-state. Chloroform molecules have been removed for clarity.

Table 3 Proton NMR data (δ) for terpyridines **1**, **2** and **3** in $CDCl_3$

Compound	δ H_1 (d)	δ H_2 (dd)	δ H_3 (dd)	δ H_4 (dd)	δ H_5 (dd)	δ H_6 (s)
1[a]	7.07	7.91	7.87	7.42	8.78	11.95
2[b]	8.03	8.62	7.85	7.33	8.69	
3[c]	7.51	8.72	8.09			

[a] N–H at 11.93 ppm. [b] OCH_3 at 4.04 ppm. [c] Data in DMSO-d_6, O–H at 11.23 ppm.

equilibrium favors the more polar keto tautomer in these solvents.[10]

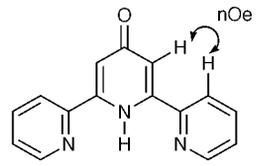
The solid-state FT-IR spectrum of **1** (Fig. 3c) contains a sharp absorption band at $\tilde{\nu}$ 3280 cm^{-1} as well as a broad band centered at $\tilde{\nu}$ 2400 cm^{-1}, both indicative of strong hydrogen bonding.[9,46] The sharp band is due to an N–H stretch of **1b** which is intramolecularly hydrogen-bonded to the nitrogen atoms of the terminal pyridine rings. The broad absorption band can be attributed to an O–H stretch of **1a**, which spans a wide range of absorption frequencies in the spectrum due to intermolecular hydrogen bonding to the carbonyl oxygen of **1b**. Both of these phenomena have already been observed in the crystal structure. This result differs from the simple 4-hydroxypyridine–pyridone system, in which the keto tautomer exists exclusively in the solid state as C=O···H–N intermolecularly hydrogen-bonded ribbons.[13] In the 4-hydroxyterpyridine–pyridone system there exist two intramolecular hydrogen bonds between the central pyridone hydrogen (H^{6k}) of the keto tautomer and the two terminal pyridine nitrogen atoms. This shields the N–H hydrogen atom and prevents it from participating in intermolecular hydrogen bonding.

The solid state FT-IR spectrum of **3**, which cannot form intramolecular hydrogen bonds, also displays a broad absorbance from $\tilde{\nu}$ 3000 to 2200 cm^{-1}, indicative of O–H···N intermolecular hydrogen bonding between the hydroxy group with the pyridine nitrogens of the enol isomer. This observation, combined with the absence of N–H and C=O stretches, indicates the existence of only the hydroxy tautomer. The comparison of **1** and **3** clearly demonstrates the ability of the terminal pyridyl rings to alter the position of the tautomeric equilibrium through hydrogen bonding.

Solution-state studies using ^{1}H NMR analysis

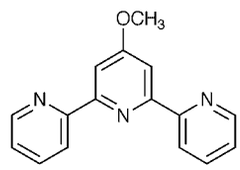
The ^{1}H NMR spectrum of **1** in $CDCl_3$ exhibits six resonances as expected for the symmetrical structure of either **1a** or **1b** (Table 3). We, however, argue that the keto isomer is the only species present in this solvent. The signals were assigned based upon coupling constants and T-ROESY experiments, which allowed the broad singlet at δ 11 to be unambiguously identified as the heteroatomic proton H(1NB) of the ketone. This assignment was based on ^{1}H NMR studies that show the N–H resonance to be solvent and concentration independent ($\Delta\delta$ less than 0.5 over a 0.1 mM to 0.1 M range). This observation can best be explained if the proton is intramolecularly hydrogen bound, and this is only possible for the keto tautomer. The protons of the terminal pyridine rings are clearly seen as four coupled resonances with peaks at δ 8.78, 7.91, 7.87 and 7.42 representing H^5, H^2, H^3 and H^4, respectively. The remaining resonance at δ 7.07 was assigned to H^1 of the central pyridone ring. This assignment was based on the presence of a nuclear Overhauser enhancement (n.O.e.) (Fig. 4) from the resonance at δ 7.07 (H^1) to that at δ 7.91 (H^2), and from a D_2O exchange experiment where this doublet at δ 7.07 collapses to a singlet upon the addition of D_2O. It is significant that this peak is shifted upfield ($\Delta\delta = -1$) with respect to unsubstituted 2,2′:6′,2″-terpyridine or the suitably *O*-methylated derivative **2**, which can be considered as a model for the hydroxy tautomer since it effectively locks the molecule into an analogous conformation. In solution, the keto tautomer **1b** can adopt a *cis–cis* conformation. This has two significant consequences: (1) it allows for the formation of two strong intramolecular hydrogen bonds between the central pyridone N–H and the nitrogen atoms on the two adjacent pyridine rings, and (2) it results in an upfield shift of H^1 due to the lack of the weak intramolecular hydrogen bonds between the H^1 protons (δ 7.07) and the nitrogen atoms of the terminal pyridine rings. The positive n.O.e. between H^1 and H^2 strengthens the case for the existence of the cisoid conformer (Fig. 4). Another probe for the tautomeric preference in solution is the notable feature that H^1 appears as a finely split doublet (J = 1.8 Hz). This splitting is not observed for compounds **2** and **3** (where **3** represents an electronically similar structure, that does not have the ability to form a bifurcated intramolecular NH···N hydrogen bond). This feature is particularly interesting as we believe it signifies *meta* coupling between H^1 and the heteroatomic proton H^{6k}, which explains the transformation of this doublet into a singlet upon the addition of D_2O. Again, this phenomenon can only hold true in the case of the keto isomer. It is important to note that the coupling of H^1 to the exchangeable proton H^{6k} eliminates the possibility that there exists a fast exchange process between the two tautomers, and provides additional proof for the presence of a single tautomer on the NMR time-scale.

Isomer **3** represents an interesting case where the less polar hydroxy tautomer is exclusively present in the solid state as well as in polar solvents (as diagnosed by FT-IR). The poor solubility of terpyridine **3** in most organic solvents limited its use as a

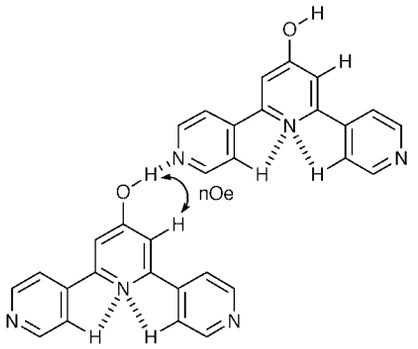


1a

Fig. 4 N.O.e. assignments for **1** in $CDCl_3$ at 25 °C.



2



3

Fig. 5 N.O.e. assignments for **3** in $CDCl_3$ at 25 °C.

model. The ^{1}H NMR of **3** in DMSO-d_6 shows a positive n.O.e. between the heteroatomic hydrogen (–OH) at 11.23 and the hydrogen on the central ring (H^1) which appears at δ 7.51 (Fig. 5). The most likely explanation for this tautomeric preference is that unfavorable steric interactions between the central N–H and the C–H atoms of the adjacent heterocycles force the three rings in **3** out of co-planarity when in the keto form. Also, the steric bulk of the terminal pyridine rings hinders the approach of the carbonyl oxygen in another molecule of **3** to hydrogen bond with the "buried" N–H. The result is that **3** isomerizes to its enol form. Only now can all three rings adopt a co-planar geometry which maximizes C–H · · · N intramolecular as well as O–H · · · N intermolecular hydrogen bonding.

An effective illustration of the influence of environment on the tautomeric equilibrium in **1** is highlighted by the variable temperature ^{1}H NMR experiments. There are no observable changes in the ^{1}H NMR spectra of **1** in $CDCl_3$ over the temperature range evaluated (25 to −80 °C).‡ On the other hand, the spectra of CD_2Cl_2 solutions display 12 resonances representing the existence of two species in a ratio of 6 : 1 at 25 °C. This ratio changes to 3 : 1 as the temperature is lowered (Fig. 6). The six predominant signals at ambient temperature closely resemble those found in the $CDCl_3$ solution spectra and were assigned to the keto tautomer **1b**. The second set of signals at δ 13.51, 8.64, 8.61, 8.00, 7.86 and 7.33 were assigned to the hydroxy tautomer **1a** based on the coupling constants and by a comparison with the chemical shifts of the *O*-methylated isomer **2** (Fig. 6c). The significant downfield shifts ($\Delta\delta$ = 1) of the singlet assigned to H^1 (δ 7.05 at 25 °C; δ 8.00 at −70 °C) and the doublet assigned to H^2 (δ 7.96 at 25 °C; δ 8.65 at −70 °C) clearly demonstrate that the terminal pyridine rings have rotated to adopt a transoid configuration in the enol form. These downfield shifts can be attributed to intramolecular hydrogen bonding between the acidic aromatic C–H protons and the basic nitrogen atoms. The broad singlet assigned to H^{6e} at δ 12.5 is shown to be temperature dependent and moves downfield ($\Delta\delta$ = 1.3) to δ 13.8 as the solution is cooled from 25 to −80 °C. The other H^{6k} resonance at δ 12.3, assigned to the N–H of the keto tautomer, does not move over this temperature range. This indicates that H^{6e} is not intramolecularly hydrogen bound (as these types of protons are concentration and temperature independent) but intermolecularly hydrogen bound. We attribute the downfield shifts of H^{6e} to an increase in the strength of the hydrogen bond between isomers as the solution is cooled. Furthermore, the large steric interactions in the transoid rotomer of **1a** prevent H^{6e} from existing as a N–H pyridone, thereby denoting the existence of the hydroxy tautomer **1a** and eliminating the existence of transoid rotamer of **1b**.

The dominance of the pyridone tautomer in $CDCl_3$ is most likely the result of both solvent effects (the stabilization of the more polar keto tautomer by the polar solvent) and substituent effects (the formation of strong intramolecular hydrogen bonds between N · · · N–H · · · N). It was unexpected that the hydroxy tautomer would increase in abundance (from 17% to 33%) as the temperature of the CD_2Cl_2 solution is lowered as it has been reported that the dielectric constant of dichloromethane increases upon cooling.[47] This implies that the more polar keto tautomer should exist exclusively at colder temperatures. However, we show that this is not the case for terpyridine **1**. We believe that the enol tautomer **1a** exists in CD_2Cl_2 because this solvent is not as effective in stabilizing the electrostatic charge built up on the carbonyl group of **1b**, shifting the tautomeric equilibrium towards the hydroxy tautomer **1a** which can be better stabilized under these conditions. The existence of **1a** provides a suitable hydrogen bond donor (the O–H hydrogen atom), which can now stabilize the electrostatic demand of the keto tautomer through hydrogen bonding. We propose that as the temperature is lowered, the system in CD_2Cl_2 begins to resemble the mixed-dimer found in the crystal.

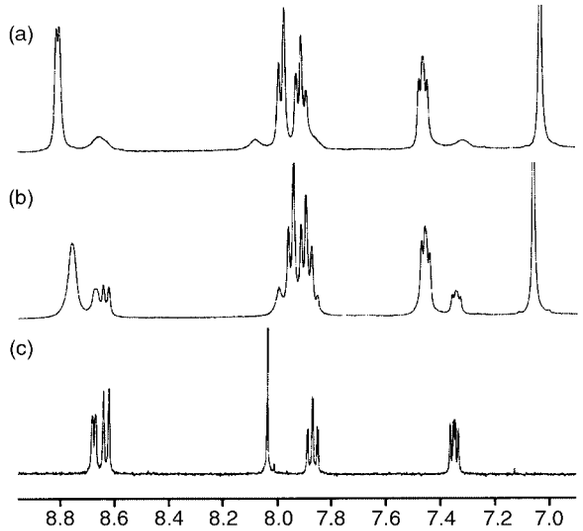


Fig. 6 ^{1}H NMR spectra of CD_2Cl_2 solutions of **1** in CD_2Cl_2 at (a) 25 °C, (b) −70 °C, and (c) **2** at 25 °C.

Conclusion

In this paper, we argue that there are three major factors governing the population distribution of terpyridine **1**. The first one concerns the choice of solvent. As has been reported for the simple 4-hydroxypyridine derivative, the more polar keto tautomer is predominant if not exclusive in polar solvents. VT ^{1}H NMR experiments uncovered an exception to this generalization, where the population of the hydroxy isomer **1a** increased as CD_2Cl_2 solutions were cooled. We rationalize this observation with the selective destabilization of the keto form. The inability of CD_2Cl_2 to effectively solvate the basic carbonyl group of **1b** through intermolecular hydrogen bonding shifts the equilibrium towards the enol form **1a** which possesses a weaker hydrogen bond donor.

We have also shown that the tautomeric equilibrium can be upset by steric factors. This was clearly demonstrated by terpyridine **3**, which exists in the hydroxy form even in very polar solvents such as dimethyl sulfoxide. In this form, all three heterocyclic rings can adopt a conformation that is close to co-planar. There is an additional stabilization resulting from intramolecular C–H · · · N hydrogen bonding. A shift to the keto form would disrupt this co-planarity because of unfavorable steric interactions of the pyridone N–H and C–H protons, destabilizing the molecule, and resulting in a preference for the hydroxy tautomer.

The third factor concerns intra- and intermolecular hydrogen

‡ There was no observable change in the ^{1}H NMR spectrum when the $CDCl_3$ was deacidified with basic alumina.

bonding. Stabilization of the keto form **1a** in polar solvents is achieved by strong bifurcated intramolecular N–H···N hydrogen bonds. In the absence of a suitable hydrogen bond donor provided by either the solvent or solute, the tautomeric equilibrium shifts and the population of the less polar hydroxy isomer grows. This is evident in the solid state as well as in CD_2Cl_2 solutions. We believe the presence of this less favorable tautomer provides a suitable hydrogen bond donor (O–H) which is able to satisfy the electrostatic demand of the basic carbonyl of **1b**.

In summary, the present study shows that solvent, hydrogen bonding and structural substituents all play a key role in affecting tautomeric distributions, illustrating the necessity of addressing all factors when designing species capable of rapid isomer interconversion.

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