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The first example of tautomerism in 2-aminopyrroles: effect of structure and solvent

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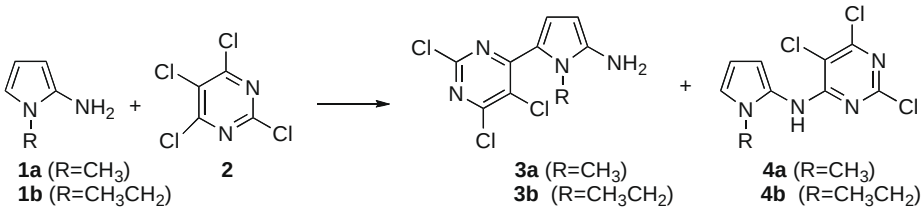
ABSTRACT

Amino/imino tautomerism is observed in secondary 2-aminopyrroles when an electron-withdrawing group is on the amino group. The amino tautomer was favored in solvents that were hydrogen bond acceptors.

Tautomerism in five-membered heterocycles, with one heteroatom, is an area of continuing interest—in particular the possibility of amino/imino tautomerism in 2-aminopyrrroles.[1] Investigators have searched for evidence of amino/imino tautomerism, in 2-aminopyrroles, without success.[2] An early report[3] for an imino tautomer was not substantiated[4] by later ^{1}H and ^{13}C NMR data. The first examples of 2-aminopyrroles, without ring substituents, have been reported[5] and isolated[6] as stable tetraphenylborate salts. NMR (^{1}H and ^{13}C) evidence indicated that only the amino form was present.[5] Theoretical calculations have concluded that the amino tautomer is the most stable form of 2-aminopyrrole;[5,7] calculations[5] on 2-amino-1-methylpyrrole predicted that both tautomers should be possible in water. In $CDCl_3$, 1-(triphenylmethyl)-3-aminopyrrole) exists solely as the imino tautomer.[8] This communication presents evidence for the long sought 2-imino tautomer; a possible structural reason for its observation is proposed, and the effect that solvents have on the tautomeric equilibrium is discussed.

Recently, we reported that the reaction of 2-amino-1-methylpyrrole (**1a**) with 2,4,5,6-tetrachloropyrimidine (**2**) gave **3a** and **4a** by addition-elimination—a new reaction pathway for 2-aminopyrroles (Scheme 1).[9] Secondary 2-aminopyrrole **4a** was isolated as an apparently pure minor product; but in its ^{1}H NMR spectrum ($CDCl_3$) there was a second component (ca. 15%). One possibility was that it was the imino tautomer.[9] Based on this observation, a detailed study has been carried out to confirm this initial assessment and to determine its generality. When the reaction was carried out with 2-amino-1-ethylpyrrole (**1b**), 2-aminopyrroles **3b** and **4b** were isolated.[10] The melting point (114–115 °C) of **4b** was indicative of a pure compound, yet its ^{1}H NMR spectrum ($CDCl_3$) indicated the presence of two species in ca. 2:1 mixture.

Figure 1a shows the aromatic region of the ^{1}H NMR spectrum of this mixture in $CDCl_3$. Seven signals, corresponding to two species, are clearly evident. The presence of the 2-amino tautomer **4b** was indicated by three multiplets and a broad NH signal (δ = 7.05 ppm) in the ^{1}H NMR spectrum. A broad CH_2 signal (δ = 6.15 ppm) and two doublets demonstrated the presence of the imino tautomer. The CH_2 signal disappeared when the spectrum was taken in solvents (CD_3OD and $(CD_3)_2CO$) where H/D exchange occurred. Another result of H/D exchange was that the coupling between C-3H and N-H, in **4b**, was lost and the C-3H multiplet collapsed to a doublet of doublets. Figure 1b illustrates these changes in CD_3OD. Because of the equilibrium indicated in Scheme 2, the vinylic protons in the imino tautomer **5b** appeared as doublets,



Scheme 1.

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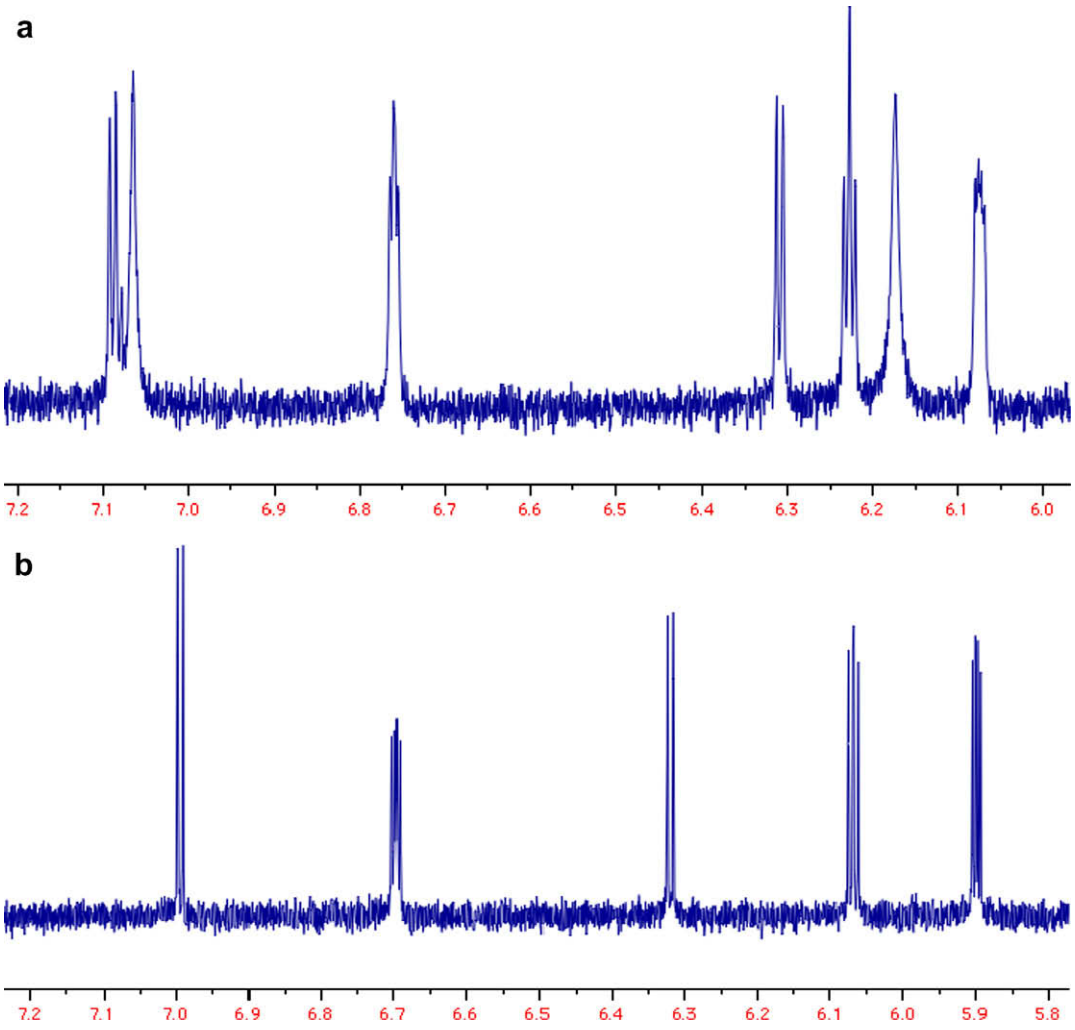
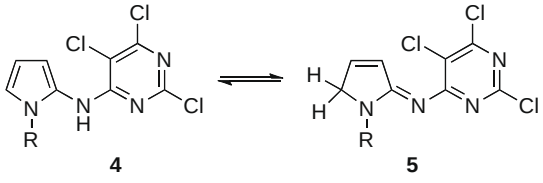


Figure 1. Proton NMR spectra of **4b**/**5b** in $CDCl_3$ (a) and CD_3OD (b).



Scheme 2.

rather than the expected multiplets, in all solvents (Fig. 1).[11] This is the first example of tautomerism in 2-aminopyrroles.[12]

As noted above, the melting points of freshly isolated **4** were indicative of a pure compound; but the NMR spectrum showed the presence of two species. One possibility was that that the initial 2-amino tautomer **4** tautomerized rapidly in $CDCl_3$. To test this, **4b** was added to frozen $CDCl_3$ and when the solvent melted, **4b** was put into the NMR at 218 K.[13] No change was noted in the amino/imino ratio compared to when dissolving it directly at room temperature. Interestingly, the proportion of the imino tautomer increased with long-term storage at -10 °C. In the case of 1-methyl **4a**, it increased from 15% to 50% and for 1-ethyl **4b** from 33% to 50% (as measured by ^1H NMR in $CDCl_3$). This would seem to suggest that tautomerization occurred in the solid state and this is why the amino/imino ratio (K_T) changed. If it had occurred in solution, the amino/imino ratio (K_T) would be expected to be a constant with time. The possibility that C–H bond breaking to give the imino tautomer is slow on the NMR time scale, but fast enough in solution for **4b** and **5b** to equilibrate, cannot be explicitly eliminated. It has been reported that 3-hydroxypyrroles exist in the keto form in the solid-state (without solvent effects), but in solution, as a solvent dependent mixture of hydroxy and keto tautomers (see below). During the variable temperature NMR study, H-5 in the 2-amino tautomer **4b**, coalesced at 218 K. The lifetime (τ was calculated using the equation $\tau = \sqrt{22}\pi\Delta\nu$, with $\Delta\nu = 4.97$ Hz and $\tau = 0.045$ s.[14]

Table 1
Effect of solvent on the tautomeric ratio K_T

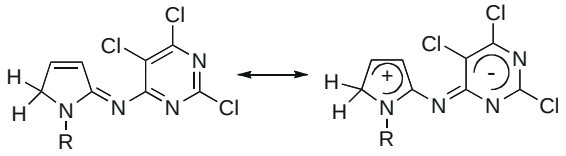
	K_T (**4b**/**5b**)
Solvent	
CD_3CN	0.8
$C_6D_5CD_3$	0.9
$CDCl_3$	1.0
CD_3OD	1.3
DMSO-d_6	1.4
DMF-d_6	1.4
$(CD_3)_2CO$	1.8

Heterocyclic tautomeric equilibria are known to be sensitive to solvent effects.[1] Amino/imino tautomerism was therefore studied in seven solvents and the results are summarized in Table 1. Values for K_T (amino/imino ratio) varied from 0.8 in CD_3CN to 1.8 in

$(CD_3)_2CO$ for **4b**. The amino tautomer was favored in solvents that were hydrogen bond acceptors. Analogous results have been reported for 3-hydroxypyrroles (hydroxy/keto).[1,15] In 2-aminothiophenes on increasing solvent polarity ($CDCl_3$ vs CCl_4) shifted the equilibrium further to the imino form; whereas, in $(CD_3)_2CO$, the amino form was favored.[16] An attempt was made to correlate K_T with the solvent parameter E_T30 (7 solvents),[17] but no correlation was found indicating that hydrogen bonding, not solvent polarity, was likely the determining factor in K_T.[15]

All previous experimental[3–5] and theoretical studies[5,7] of amino/imino tautomerism in 2-aminopyrroles have been carried out with compounds with *primary* amino groups. The compounds of interest in this communication are *secondary* 2-aminopyrroles without further substitution on the pyrrole ring. A literature search revealed that almost all previously reported secondary 2-aminopyrroles had at least two other substituents on the pyrrole ring. Prior[18] to our recent report[19] of the solid-state synthesis of secondary 2-aminopyrroles, there had been only a few reports of this type of derivative without further substitution on the pyrrole ring. And there are no other examples of 2-aminopyrroles substituted only at the *exo* amino group by an aryl or heteroaryl substituent in the literature. No imino tautomer was detected by ^{1}H NMR when the heteroaryl substituent was on C-5 (2-aminopyrroles **3**) or on C-3 (R = *t*-butyl).[9] Only when the trichloropyrimidine substituent was on the *exo* amino group was the imino tautomer detected. This would seem to suggest that conjugation of the imino nitrogen with the trichloropyrimidine ring was necessary to observe tautomerism.

Tautomerism in heteroaromatic systems can be explained by comparing the relative stability of the possible tautomeric forms.[1] Only when the tautomeric forms are of comparable stability will a tautomeric equilibrium be evident. No tautomerism was detectable by ^{1}H NMR when the amino substituent was an alkyl group[19], or the trichloropyrimidine substituent[9] was not on the amino group. Conjugation of the imino nitrogen with the trichloropyrimidine ring would appear to have stabilized the imino tautomer relative to the amino tautomer. Such conjugation would result in polar resonance contributors. The resonance hybrid (**6**) of the polar contributors of **5** can be seen below. The strong electron withdrawing effect of the trichloropyrimidine ring would be expected to stabilize these resonance contributors.



5 **6**

2-Aminothiophene exists as the amino form, but secondary amino derivatives exist as solvent-dependent tautomeric mixtures (amino/imino) when there was an electron-donating substituent present at C-3 of the thiophene ring.[16] Electron-withdrawing groups on C-2 favor the hydroxy form in 3-hydroxypyrroles.[15,20] The results of this study and with 2-aminothiophenes suggest that amino/imino tautomerism can be expected when the secondary amino derivative contains a substituent that can stabilize the polar resonance contributors of the imino tautomer. In the case of 2-aminopyrroles **4**, a push-pull effect was present—the strong electron-donating ability of the ring nitrogen was buttressed by the electron-withdrawing effect of the trichloropyrimidine ring.

Acknowledgments

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10. A mixture of the 1-ethyl-2-aminopyrrole tetraphenylborate salt[6] (378.8 mg, 0.88 mmol) and 2,4,5,6-tetrachloropyrimidine (174.4 mg, 0.800 mmol) was dissolved in THF (2.00 mL), and Et_3N (0.345 mL, 2.47 mmol) was added. The reaction mixture was stirred in the dark for 3.75 h and THF was removed with a stream of nitrogen gas. The resulting solids were dissolved/suspended in a minimum amount of CH_2Cl_2. Flash column chromatography (silica gel) using gradient elution starting with pure petroleum ether (35–60 °C) and ending with pure CH_2Cl_2 gave two components that were further purified by subsequent chromatography (9:1 CH_2Cl_2/petroleum ether (35–60 °C)). 1-Ethyl-5-(4,5,6-trichloropyrimidin-2-yl)-1*H*-pyrrol-2-amine (**3b**) was recrystallized from ethanol and water (74.7 mg, 32%); mp = 172–173.5 °C. 4,5,6-Trichloro-*N*-(1-ethyl-1*H*-pyrrol-2-yl)pyrimidin-2-amine (**4b**) (15.2 mg, 7%) isolated as a yellow oil and recrystallized from petroleum ether (35–60 °C); mp = 114–115 °C. NMR data is given below.
11. Compound **4b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (br, 1H), 6.75–6.74 (dd, 1H, J = 3.04 Hz, J = 1.92 Hz), 6.22–6.21 (t, 1H, J = 3.4 Hz, J = 3.04 Hz), 6.07 (br m, 1H), 3.80–3.75(m (overlaps with CH_2 of **5b**), 2H), 1.44−1.39 (m (overlaps with CH_3 of **5b**) 3H). Compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09−7.08 (d, 1H, J = 3.9 Hz), 6.30−6.29 (d, 1H, J = 3.9 Hz), 3.80–3.75 (m (overlaps with CH_2 of **4b**), 2H), 1.44−1.39 (m (overlaps with CH_3 of **4b**) 3H). Compound **4b**: ^{1}H NMR (300 MHz, CD_3OD): δ 6.70–6.93 (dd, 1H, J = 3.08 Hz, J = 1.88 Hz), 6.08–6.06 (dd, 1H, J = 3.67 Hz, J = 3.08 Hz), 5.94–5.89 (dd, 1H, J = 3.08 Hz, J = 1.88 Hz), 3.82–3.78 (q, 2H, J = 7.29 Hz), 1.33−1.30 (t, 3H, J = 7.29 Hz). Compound **5b**: ^{1}H NMR (300 MHz, CD_3OD): δ 7.00−6.99 (d, 1H, J = 4.0 Hz), 6.32−6.31 (d, 1H, J = 4.0 Hz), 3.76–3.71 (q, 2H, J = 7.26 Hz), 1.32−1.29 (t, 3H, J = 7.26 Hz).
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