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Multiple hydrogen bonds and tautomerism in naphthyridine derivatives

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The behaviour of three 2,7-disubstituted 1,8-naphthyridines able to exhibit tautomerism has been studied by NMR in solution and in two cases in the solid state. The three derivatives studied are 2,7-dihydroxy- (**1**), 2-acetamido-7-amino- (**3**) and 2,7-diacetamido-1,8-naphthyridine (**4**). To explore the problem of secondary interactions, a series of complexes, with up to four simultaneous hydrogen bonds, where the monomers are generated using pyridine and 4-pyridone as building blocks, have been theoretically studied. The calculated interaction energies have been correlated with the number of hydrogen bonds and with attractive and repulsive secondary interactions. Further analysis of the electron density and orbital interactions shows that the secondary interactions, both attractive and repulsive, have a purely electrostatic origin. The X-ray structure of compounds **3** and **4** have been determined. In the solid state these compounds exist in the "diamino" tautomers with the N–H proton of the amido groups pointing towards the naphthyridine nitrogen. DFT and GIAO calculations have been essential to disentangle the problem of the structure of these compounds.

Introduction

The relationship between tautomerism and intramolecular hydrogen bonds (IMHB) is well-known.[1] Obviously, an IMHB stabilises the tautomer that presents it in comparison with other tautomers where the IMHB is not possible. Depending on the strength of the HB, 12–20 kJ mol^{-1} of extra stabilisation is brought by each HB.[1] On the other hand, the information about the effect of intermolecular hydrogen bonds on tautomerism is scarce. These HBs are of paramount significance in the solid state while in solution the situation is more complex because usually there are several possible associations that exist in dynamic equilibrium. We have studied theoretically the case of hydrogen-bonded dimers of 2-hydroxypyridine as well as a series of 2-aminopyridines, showing that dimerisation can shift the tautomeric equilibria towards the less stable tautomer.[2]

A related problem is the possible existence of solid state proton transfer (SSPT), which requires both hydrogen-bonded associations and quasi-degenerate equilibria: typical examples are benzoic acids[3] and symmetric NH-pyrazoles.[4] In both cases, the energy of the system before and after the multiple (n = 2, 3 or 4) proton transfer should be identical or nearly identical for the SSPT to occur.

Finally, a third problem appears when there are several intermolecular hydrogen bonds in a complex: the non-additivity of their effects. A large number of important biological processes are mediated by multiple hydrogen bond recognition. Nucleic acid base pairs in their Watson–Crick configuration show two (adenine–thymine) or three (guanine–cytosine) simultaneous HBs. Jorgensen *et al.* were the first to notice the influence of the relative disposition of the donor and acceptor groups on the interaction energy of the complexes. Thus, while the guanine–cytosine and uracil–2,6-diaminopyridine pairs show the same number and type of HBs, the interaction energy of the first complex is double that of the second (−92.5 *vs.* −47.7 kJ mol^{-1}).[5,6] Using theoretical calculations, this group justified this result on the basis of secondary attractive or repulsive electrostatic interactions. These observations were used by Jeong *et al.* to explain differences in imide–imide, imide–lactam, and lactam–lactam host-guest chemistry.[7,8] There are several experimental studies of multiple hydrogen-bonded systems associated with the disposition of the acceptors and donors. A series of triply hydrogen-bonded complexes with a variety of motifs was shown to produce a large range of association constants.[9] Sartorius and Schneider have examined the ΔG of fifty-eight dimers formed by nucleobases and synthetic host-guest complexes.[10] Complexes with up to four simultaneous HBs have been explored by Meijer *et al.*[11] and by Lünig and Kühl.[12] The simultaneous effect of the HB pattern and tautomeric equilibrium of ureidopyrimidones as a function of the substituents has also been studied.[11] More recently, several reviews[13–15] have gathered other experimental examples showing the importance of multiple HBs in molecular recognition. Since this approach has been criticised by Lukin and Leszczynski[16] and by Popelier and Joubert[17] as

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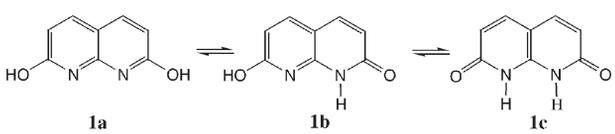
an oversimplification, we will compare their conclusion to ours. In addition, AIM theory will be used to characterise these weak interactions.[18]

Results and discussion

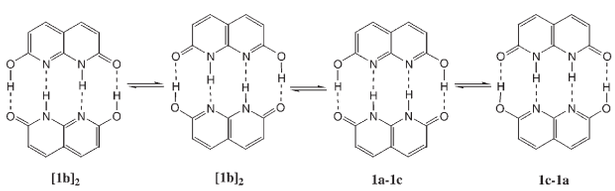
The case of dione 1 and the problem of multiple hydrogen bonds

Our first idea was to find other systems able to sustain SSPT using several hydrogen bonds and we focused on 2,7-dihydroxy-1,8-naphthyridine (**1**). This compound presents three tautomeric forms, **a** (dihydroxy), **b** (oxo/hydroxy) and **c** (dioxo).



1a **1b** **1c**

Two kinds of dimers with four HB are possible: two degenerate homodimers $[\mathbf{1b}]_2$ (left/right permutation) and two degenerate heterodimers **1a**–**1c** (up/down permutation).



$[\mathbf{1b}]_2$ $[\mathbf{1b}]_2$ **1a-1c** **1c-1a**

Both pairs fulfil the necessary condition for SSPT since after the transfer of four protons, the initial and final states are identical. This compound was known.[19] We prepared it but it is very insoluble and we have been unable to obtain either suitable single-crystals or microcrystalline powder: in all our attempts an amorphous material was isolated. Because of this, the study of its tautomerism is based on NMR measurements in solution together with theoretical calculations. At the B3LYP/6-31+G** level, the most stable tautomer is the oxo/hydroxy **1b** ($E_{rel} = 0.0$ kJ mol^{-1}) followed by the dioxo **1c** ($E_{rel} = 10.1$ kJ mol^{-1}), the less stable being the dihydroxy **1a** ($E_{rel} = 34.6$ kJ mol^{-1}). In DMSO solution, the NMR spectra correspond to a molecule of C_{2v} symmetry. The signal at 112.0 ppm has $^1J = 168.6$ Hz while that at 139.4 ppm has two couplings, $^1J = 162.9$ Hz and $^3J = 3.6$ Hz (Scheme 1).

To determine the tautomer responsible for the above spectrum, we have calculated with the GIAO program (B3LYP/6-31+G**/B3LYP/6-31G*; for programs and packages, see the computation section in the Experimental) the ^{13}C absolute shieldings of the three tautomers and transformed them into chemical shifts by the relationship $\delta^{13}C = 188.10 - \sigma^{13}C$ (with δ values in ppm), 188.10 being the absolute shielding of TMS at the same level. In order to have more points for the comparison, we have included the five carbons of 2-pyridone determined in the same solvent.[20] The calculated shifts of tautomers having a C_{2v} symmetry, **1a** and **1c**, do not agree with the experimental ones. There are two possibilities that agree well with the calculated values: a near 50/50 mixture of **1a** and **1c** in equilibrium ($K_T \approx 1$) and a degenerate equilibrium between **1b** and an identical **1b** tautomer (Scheme 1). We prefer this last hypothesis for the following reason: **1a** is much less stable than the other tautomers and thus a mixture with **1c** should not have equal proportions in solution. A comparison based on TMS, pyridone and an averaged **1b** leads to eqn. (1):

$$\delta^{13}C(\text{expt}) = (0.929 \pm 0.006)\delta^{13}C(\text{calc}) \quad (\text{with } n = 11,\ r^2 = 1.000) \qquad (1)$$

and to the fitted values reported in Scheme 1. Moreover, according to the B3LYP/6-31+G**//B3LYP/6-31G* calculations concerning the dimers, $[\mathbf{1b}]_2$ is more stable than **1a**–**1c** (or **1c**–**1a**) by 14.4 kJ mol^{-1}.

To understand the influence of the four hydrogen bonds present in dimers of compound **1**, we turn now to the problem of the secondary interactions. To approach this problem, a set of supermolecules built up by adding 4-pyridone and pyridine fragments, as HB donor and acceptor respectively, has been selected to generate a set of twelve dimers with up to four such fragments in each interacting molecule (Scheme 2). The presence of a HB donor has been denoted with a "**1**" and that of a HB acceptor with a "**0**" (for instance, **00** represents 1,8-naphthyridine). In Scheme 3, some of the systems with one, two and three fragments are shown.

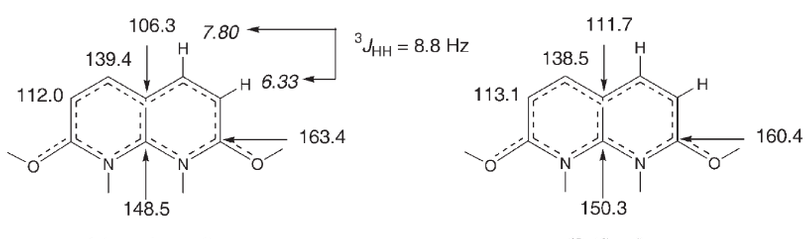
Like all energy partitions, the Jorgensen approach[5,6] has been subject to criticism.[16,17] However, this kind of approach, used with caution, may allow an estimation of non-calculated situations; besides, our model compounds are very different from those of Lukin and Leszczynski who used a series of seventeen different complexes,[16] and from those of Popelier and Joubert, whose analysis is based on twenty-seven natural DNA base pairs.[17]

Even though the systems have been selected to be able to form similar HBs with all their potential centres, this did not happen due to the concave curvature of the interacting rim of the molecules. In general, the end HBs are shorter than the central ones (Table 1). A clear example of this trend is the complex **1111**–**0000** where the HBs distances are 1.97 and 2.32 Å in the end and central positions, respectively. The interaction energies of the calculated complexes (Table 1) show that cases with similar number of HBs (x_1) and attractive (x_2) and repulsive (x_3) interactions present differences of up to 9.9 kJ mol^{-1}.

Initially, two models have been tried to correlate the interaction energy and the mentioned parameters, x_1, x_2 and x_3. In the first model, given in eqn. (2):

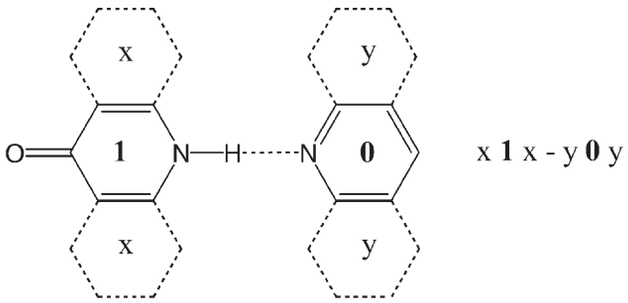
$$E_{I+BSSE} = -(28.35 \pm 0.69)x_1 - (6.46 \pm 0.70)(x_2 - x_3) \quad (\text{with } n = 12,\ r^2 = 0.96) \qquad (2)$$

it has been considered that the absolute value of both secondary interactions are the same, independent of whether they are attractive or repulsive, as proposed by other authors.[5,6,10]



1 (experimental) **1b** (fitted)

Scheme 1 Comparison of experimental ^{1}H and ^{13}C chemical shifts for compound **1** with those fitted to **1b** (^{13}C).



Scheme 2 Schematic representation of the compounds considered.

In the second model, defined by eqn. (3):

$$E_{\mathrm{I+BSSE}} = -(31.24 \pm 5.73)x_1 - (4.43 \pm 4.05)x_2 + (8.48 \pm 4.05)x_3 \ (\text{with } n = 12,\ r^2 = 0.96) \quad (3)$$

the attractive and repulsive interactions are independently considered; note that the average of coefficients of x_2 and x_3 coincides with the coefficient of $(x_2 - x_3)$ in eqn. (2).

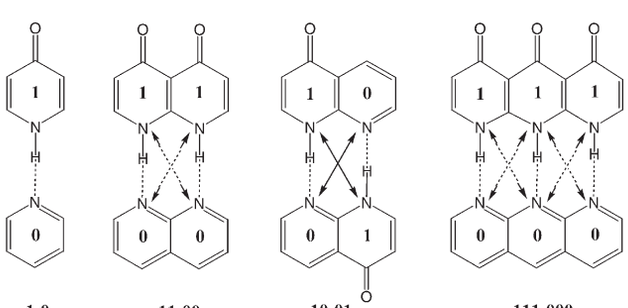
These models assume that all the individual HBs contribute the same stabilising energy despite their different interaction distances. Thus, the complexes with HB distances above that of the average of the whole set (2.02 Å) show positive deviations and those with shorter HB distances show negative deviations. A way to generate a weighted number of HBs is to divide the average distance of the whole set by each particular HB distance and add the resulting values to provide a new parameter x_1'. Thus, for example, the corrected number of HBs for complex **1111–0000** is 3.78 and for the **1100–0011** one, 4.12. The new correlations in eqns. (4) and (5):

$$E_{\mathrm{I+BSSE}} = -(28.35 \pm 0.50)x_1' - (6.81 \pm 0.50)(x_2 - x_3) \ (\text{with } n = 12,\ r^2 = 0.98) \quad (4)$$

$$E_{\mathrm{I+BSSE}} = -(32.38 \pm 3.80)x_1' - (4.03 \pm 2.65)x_2 + (9.70 \pm 2.74)x_3 \ (\text{with } n = 12,\ r^2 = 0.98) \quad (5)$$

slightly improve the results of eqns. (2) and (3).

The results obtained are comparable to those obtained by Jorgensen *et al.* [−31.4 kJ mol^{-1} for each HB and ±10.5 kJ mol^{-1} for each secondary interaction, *cf.* eqns. (2) and (3)] in their theoretical papers.[5,6] However, with the present set of data, which allows a more detailed analysis, the repulsive secondary interactions have twice the value of the attractive ones [eqns. (3) and (5)]. Lukin and Leszczynski[16] reported values of −14.4 and +5.7 kJ mol^{-1} for the HB and the repulsive interaction (no attractive interactions in their model), values that are to be compared with ours from eqn. (5): −32.8 and +(9.7 ± 2.7) kJ mol^{-1}, respectively. The HB contribution is not comparable as the systems are very different, but the repulsive one is similar, although probably underestimated. Popelier and Joubert's main conclusions were: (i) that secondary interactions cannot be invoked to explain the pattern of natural base pair stability and (ii) that only in comparisons between highly similar chemical environments could the secondary interactions be invoked for the right reason. This last point applies to our approach.



Scheme 3 Some examples of the complexes studied and nomenclature used with one, two and three HBs. Attractive secondary interactions are shown by dashed double arrows and repulsive ones by continuous double arrows.

Table 1 Interaction energy, HB distance and the number of attractive and repulsive secondary interactions for all the complexes studied

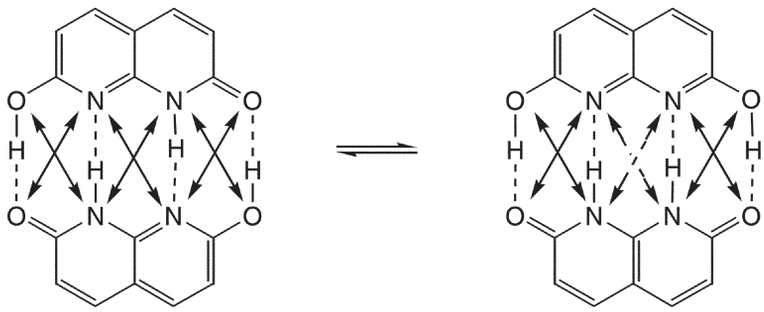
System	$E_{\mathrm{I+BSSE}}$/ kJ mol^{-1}	HB distance[a] /Å	Secondary interactions: Attractive (x_2)	Secondary interactions: Repulsive (x_3)
1-0	−32.39	1.991	0	0
11-00	−69.91	2.038, 2.038	2	0
10-01	−46.14	1.955, 1.955	0	2
111-000	−106.98	2.016, 2.204, 2.016	4	0
100-011	−91.66	1.881, 2.052, 1.930	2	2
101-010	−56.34	1.969, 2.078, 1.969	0	4
1111-0000	−139.33	1.970, 2.319, 2.319, 1.970	6	0
1001-0110	−99.59	1.845, 2.100, 2.100, 1.845	2	4
1010-0101	−70.69	1.902, 2.156, 2.156, 1.902	0	6
1110-0001	−132.66	1.904, 2.192, 2.127, 1.801	4	2
1101-0010	−93.41	1.911, 2.183, 2.148, 1.931	2	4
1100-0011	−142.59	1.837, 2.091, 2.091, 1.837	4	2

[a] For each system, $x_1x_2\ldots$–$y_1y_2\ldots$, the HB distances are given in the order $x_1\ldots y_1$, $x_2\ldots y_2$ and so on.

The AIM analysis shows the presence of a bond critical point (bcp) for each HB formed with values in the range 0.086–0.014 e a.u.$^{-3}$. In addition, ring critical points due to the HBs are obtained. However, no indication of a bcp is obtained for the attractive secondary interactions, which is the main criteria used to characterise HB interactions by Koch and Popelier.[18] A topological analysis of the complexes does not show any significant difference between those with attractive and repulsive secondary interactions. In a previous article, we have shown that bifurcated HBs[21] can be characterised based on the AIM methodology but they are not found in the complexes studied here. The NBO analysis of the HB complexes shows an interaction between the lone pair of the nitrogen atom (HB acceptor) with the antibonding N–H orbital of the amino HB donor. In the present case, the interaction energies of these two orbitals are quite strong, up to 101.2 kJ mol^{-1}. However, no orbital interaction is observed that could justify the secondary attractive interactions found.

Since no bond critical point and orbital interaction is observed, the stabilising (or repulsive) secondary interactions can only be explained on the basis of a pure electrostatic model. Computing a simple electrostatic model that considers the charges on the hydrogen (N–H of pyridone) and on the nitrogen (=N– of pyridine), we obtained stabilising and repulsive energies with the correct sign although ten times larger than the ones calculated with our models [eqns. (3) and (5)].

If we come back to compound **1** (Scheme 4), the secondary interactions should favour the heterodimer **1a**–**1c** over the homodimer [**1b**]$_2$. It is possible to carry out the following simple calculation. From the values for the monomers (**1b** 0.0; **1c** 10.1 and **1a** 34.6 kJ mol^{-1}), the dimers should have [**1b**]$_2$ 0.0 and **1a**–**1c** 44.7 kJ mol^{-1}, but the calculation of the dimers yields [**1b**]$_2$ 0.0 and **1a**–**1c** 14.4 kJ mol^{-1} (the difference being 44.7–14.4 = 30.3 kJ mol^{-1}). Concerning the secondary



[1b]$_2$ **1a-1c**

Six repulsive Two attractive and four repulsive

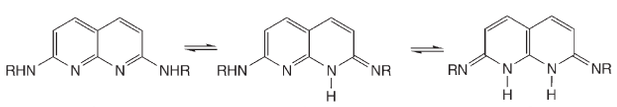
Scheme 4 Secondary interactions in the 2,7-dihydroxy-1,8-naphthyridine dimers (dashed = attractive, continuous = repulsive).

interactions, on going from **[1b]$_2$** to **1a**–**1c**, two repulsive interactions become two attractive interactions. Thus, 30.3/2 = 15.15 kJ mol^{-1} corresponds to the transformation of one repulsive into one attractive interaction. This is not far from the 13.7 kJ mol^{-1} from eqn. (5).

In conclusion, a **[1b]$_2$** structure seems reasonable to correspond to the solid state and still is a good candidate for SSPT. Substituents on symmetrical positions of the naphthyridine ring are probably necessary to obtain compounds with improved physical properties (lower melting points, better solubilities, and easier crystallisation).

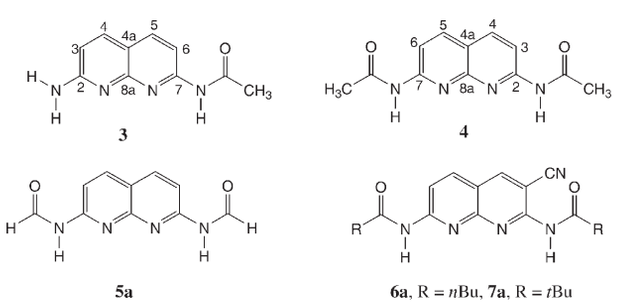
The case of the diamino derivatives

We turn now to the related compounds, the 2,7-diamino-1,8-naphthyridines **2**. The problem is very similar and dimers like **[2b]$_2$** or **2a**–**2c** could be expected. Note, however, that the tautomerism amine/imine is much more shifted to the "aromatic" amino form than the tautomerism hydroxy/oxo to the corresponding "aromatic" hydroxy form.[1]



2a **2b** **2c**

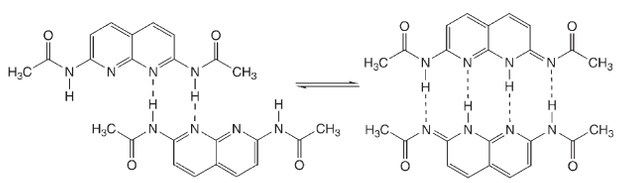
To increase the acidity of the 2,7-amino groups (R = H), thus enhancing the stability of the "imino" tautomers, we decided to study derivatives in which at least one R = $COCH_3$. Two compounds were first prepared, 2-acetamido-7-amino-1,8-naphthyridine (**3**) and 2,7-diacetamido-1,8-naphthyridine (**4**), and the possible formation in the solid state of homo- **[3b/4b]$_2$** and heterodimers **3a/4a**–**3c/4c** was examined. We have already reported computational studies of the formation of hydrogen-bonded heterodimers involving a derivative of compound **2** with R = CHO (**5**).[21] Derivatives of **4** (**6**, R = *n*Bu and **7**, R = *t*Bu)[5,6,16] have been used to study the formation of heterodimers with ureas in solution; the results obtained point to the formation of four HBs while the dimer of the diamino tautomer is not observed (probably because it can form only two HBs).[22] Other authors have used 2-acetamido-1,8-naphthyridines as artificial receptors.[23]



3 **4**

5a **6a**, R = *n*Bu, **7a**, R = *t*Bu

Even if the diamino tautomer **a** is more stable than the amino-imino one **b**,[22] the first can form only two HBs with itself while the second could form four HBs, and according to our calculations on 2-aminopyridines, this may be enough to modify the equilibrium towards **[4b]$_2$**.



[4a]$_2$ **[4b]$_2$**

The ^{1}H and ^{13}C NMR spectra of the acylamino derivatives **3** and **4** were recorded in CD_3OD. Due to the minute quantities of compounds available, the ^{13}C chemical shifts were obtained with difficulty. The results are reported in Table 2.

Crystallography

We never succeeded in obtaining crystals of compound **1**, but the structures of the two other naphthyridines **3** and **4** have been solved. Compound **3** exists in the diamino form **3a** with the acetamido group in the normal *Z* configuration and the N–H pointing towards the lone pair of the naphthyridine nitrogen. The hydrogen-bond network is rather complicated and involves all the N and O atoms connecting four molecules throughout three conventional HBs, N(1) to N(3) and N(4) to O(1) and N(2). Interestingly, O(1) participates in two short C–H interactions, one intramolecular to C(4) and one intermolecular to C(8) (see Fig. 1 and Scheme 5). Some of these H-bonding features are retained in structure **[4a]$_2$**.

Putting aside the complexity introduced by the water molecule, compound **4** crystallises also as "diamino" tautomer **a**, both acetamido groups being of configuration *Z*. Classical HBs linking N(1) to N(3) and N(4) to N(2), similar to those

Table 2 NMR chemical shifts (ppm) and coupling constants (Hz) of the 2,7-diamino-1,8-naphthyridines **3** and **4** in CD_3OD

	3	**4**
2, 7	C2: 154.7, C7: 162.7	C: 154.9
3, 6	C3: 111.2, C6: 112.8; H3: 8.01, H6: 6.77, ^3J = 8.8	C: 114.9; H: 8.29, ^3J = 8.8
4, 5	C4: 140.0, C5: 139.2; H4: 8.01, H5: 7.89, ^3J = 8.8	C: 140.1; H: 8.27, ^3J = 8.8
4a	116.0	119.3
8a	156.4	155.6
C=O	170.5	172.4
CH_3	C: 22.5; H: 2.23	C: 24.2; H: 2.25

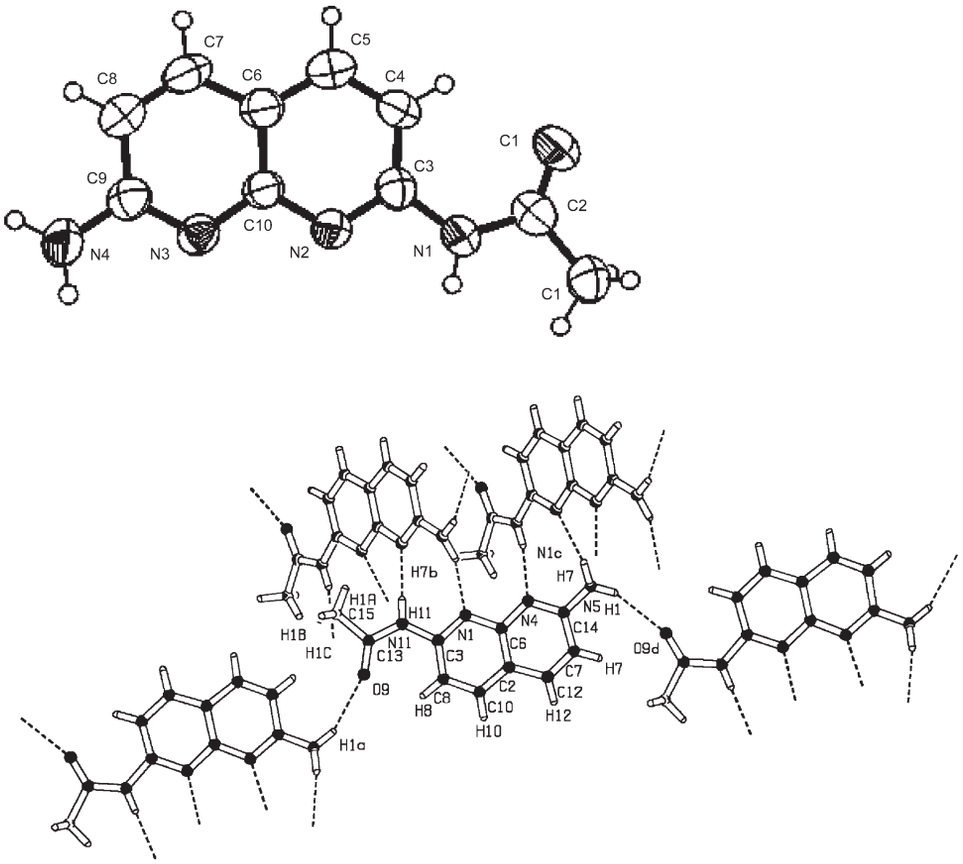
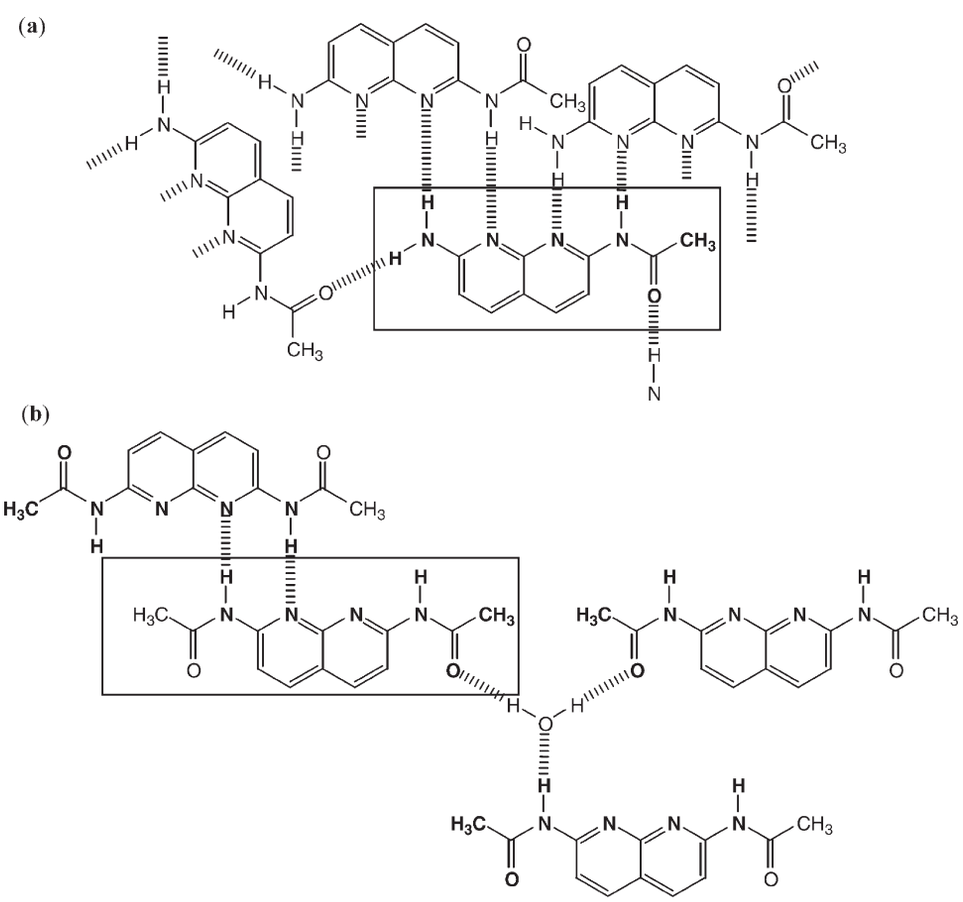


Fig. 1 The molecular structure of **3a** and **4a**.



Scheme 5 The hydrogen-bond network present in **3a** and **4a**.

found in compound **3a**, are recognised in structure **4**. The water molecule adds three HBs linking three molecules, accepting one HB from the N(4) and donating HBs to the O(2) atoms of two different molecules. Both naphthyridine molecules show two short intramolecular C–H···O interactions similar to those found in **3a**.

DFT calculations

The relative values of the energy E_{rel} of the different pairs of tautomers derived from symmetrically 2,7-disubstituted 1,8-naphthyridines **2**, not only that of the compound here reported, **4**, but also those of possible future candidates are reported in Table 3. In all cases the "diamino" (actually, in general the diacylamino) tautomer is more stable than the "amino/imino" one; this is the reason why the third tautomer, the "diimino" **2c**, was not calculated. In the case of the cyanamido derivative, the **2b** tautomer is more stable than the "diamino" one. In three cases, the equilibrium has also been calculated for the corresponding pyridines (NH_2, $NHNO_2$ and NHCN).[2] The values for the naphthyridines are roughly proportional to those of the pyridines [eqn. (6)]:

$$E_{rel}(\text{naphthyridines}) = -(5.0 \pm 1.7) + (0.76 \pm 0.19)\, E_{rel}(\text{pyridines}) \quad (\text{with } n = 3,\ r^2 = 0.94) \qquad (6)$$

^{13}C GIAO calculations on compounds **3** and **4** were carried out on the "diamino" forms **a** and compared with the experimental values in Table 2. Here also, the five points corresponding to 2-aminopyridine were included in the comparison [eqn. (7)]:[24]

$$\delta^{13}\text{C(expt)} = (1.076 \pm 0.004)\delta^{13}\text{C(calc)} \quad (\text{with } n = 23,\ r^2 = 1.000) \qquad (7)$$

The slope is slightly different than in eqn. (1), probably due to the difference in solvents, DMSO and methanol, respectively. In any case, these compounds exist predominantly in the aromatic "diamino" form **a**.

Concluding remarks

The existence of multiple hydrogen bonds is essential for replication and recognition in both DNA and RNA. From the third HB onwards, the stabilisation is no longer additive. To analyse these non-pairwise effects we have used a theoretical model based on pyridine and 4-pyridone derivatives that has allowed us to estimate that the repulsive secondary interactions are two times larger than the attractive ones (+9 *vs.* −4 kJ mol^{-1}). This model has been used to rationalise the case of 2-oxo-7-hydroxy-1,3-dihydro-1*H*-naphthyridine (**1b**), a compound existing in the solid state probably as the [**1b**]$_2$ dimer with four intermolecular HBs and having the possibility to sustain SSPT. Unfortunately, the amide derivatives **3** and **4** do not exist as amino/imino tautomers **b** but as the diamino (diacylamino) tautomers **a** and, therefore, cannot present the four HBs necessary for SSPT. Their system of HBs is, nevertheless, interesting and show that these kinds of molecules deserve further consideration, for instance, replacing the CH_3 groups by CF_3 in **4**.

Table 3 Calculated relative energies E_{rel} of tautomeric pairs. **2a** is always more stable than **2b**

R	E_{rel}/kJ mol^{-1}
H (amino)	21.3
HCO (formamido, **5**)	32.5
CH_3CO (acetamido, **4**)	30.8
CF_3CO (trifluoroacetamido, **8**)	23.3
O_2N (nitramino)	8.6
NC (cyanamido)	15.9

Experimental

Syntheses

2,7-Dihydroxy-1,8-naphthyridine (**1**) was prepared according to Newkome *et al.*[25] The starting 2,7-diamino-1,8-naphthyridine was prepared according to Zimmerman *et al.*[26] These authors also described an example of *N*,*N*′-diacylation using valeric anhydride and triethylamine (yielding 2,7-NHCOC$_4$H$_9$-1,8-naphthyridine).

Compounds 3 and 4. A mixture of 2,7-diamino-1,8-naphthyridine (100 mg, 0.625 mmol) and acetic anhydride (1 mL) was heated at 60 °C for 6 h. Acetic anhydride and acetic acid were then removed under reduced pressure and the resulting solid was washed with 5% sodium bicarbonate solution and extracted with dichloromethane. Solvent was removed and a white solid was obtained (150 mg). By crystallisation two compounds were obtained, the monoacetylated derivative **3** and the diacetylated derivative **4**. **3**: yield 37%; m.p. 261–263 °C; anal. calcd for $C_{10}H_{10}N_4O$: C 59.40, H 4.98 N 27.71; found C 59.37, H 4.92, N 27.93. **4**: yield 58%; m.p. 238–240 °C; anal. calcd for $C_{12}H_{12}N_4O_2$: C 59.01, H 4.95 N 22.94; found C 58.77, H 5.03, N 22.81.

NMR spectroscopy

NMR spectra were recorded on a Bruker DRX 400 spectrometer (9.4 Tesla, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C). Chemical shifts (δ) are given relative to the solvent: CD_3OD 3.31 ppm for ^{1}H and 49.2 ppm for ^{13}C, DMSO-d_6 2.49 ppm for ^{1}H and 35.9 ppm for ^{13}C. 2D inverse proton detected heteronuclear shift correlation spectra, gs-HMQC (^{1}H-^{13}C) and gs-HMBC (^{1}H-^{13}C) were obtained using standard pulse sequences.[27] For compound **1** (20 mg, solvent DMSO-d_6) the ^{1}H, ^{13}C-CPD, ^{13}C NMR coupled spectra were measured and assigned by analogy with pyridones.[20] For compound **4** (2 mg, solvent CD_3OD) the ^{1}H, (^{1}H-^{13}C) gs-HMQC, (^{1}H-^{13}C) gs-HMBC, ^{13}C chemical shifts were measured and assigned

Table 4 Crystal data and structure refinement for **3a** and **4a**

	3a	**4a**
Empirical formula	$C_{10}H_{10}N_4O$	$2(C_{12}H_{12}N_4O_2)\cdot H_2O$
Formula weight	202.22	506.53
Temperature/K	293(2)	200(2)
Wavelength/Å	1.5418	1.5418
Crystal system	Orthorhombic	Monoclinic
Space group	*Fdd*2	*P*21/*c*
a/Å	19.001(3)	27.8630(5)
b/Å	25.829(8)	11.4857(2)
c/Å	7.844(2)	7.5182(1)
α/°	–	93.915(1)
U/Å^3	3850(2)	2400.41(7)
Z	16	4
μ/mm^{-1}	0.790	0.846
Reflections collected	2690	26 311
Unique reflections	1431	4481
R_{int}	0.0712	0.0660
R_1 [$I > 2\sigma(I)$]	0.048	0.046
wR_2 [$I > 2\sigma(I)$]	0.099	0.122
R_1 (all data)	0.085	0.068
wR_2 (all data)	0.118	0.165
Absolute structure parameter	0.5(6)	–

Table 5 Relevant hydrogen bond features for **3a** and **4a**

D—H···A	D–H/Å	H···A/Å	D···A/Å	D–H···A/°	Symmetry[a]	Structure
Similar features for **3a** and **4a**						
N1–H1···N3	0.860(4)	2.131(3)	2.974(5)	166.4(3)	3-2	**3a**
N1A–H11A···N3B	0.86(3)	2.32(3)	3.180(3)	171(2)		**4a**
N4–H4A···O1	0.90(6)	2.33(6)	3.180(5)	158(5)	3-1	**3a**
N4A–H44A···O10	0.98(3)	2.01(3)	2.986(3)	169(3)		**4a**
N4–H4B···N2	0.97(5)	2.19(5)	3.130(6)	163(4)	3-3	**3a**
N4B–H44B···N2A	0.98(3)	2.23(3)	3.231(3)	173(3)		**4a**
C4–H4···O1	0.930(4)	2.268(3)	2.854(5)	121.2(3)		**3a**
C4A–H4A···O1A	0.93(3)	2.21(3)	2.827(3)	124(2)		**4a**
C4B–H4B···O1B	1.01(3)	2.22(3)	2.847(3)	119(3)		**4a**
C8A–H8A···O2A	0.97(3)	2.19(3)	2.840(3)	123(2)		**4a**
C8B–H8B···O2B	0.94(3)	2.22(3)	2.836(3)	123(2)		**4a**
Specific features for **3a** and **4a**						
C8–H8···O1	0.9300	2.5700	3.364(6)	144.00	3-1	**3a**
N1B–H11B···O1A	0.91(3)	1.97(3)	2.865(3)	170(2)	4-2	**4a**
O10–H10A···O2A	0.914	1.967	2.852(3)	162.4(1)	4-1	**4a**
O10–H10B···O2B	0.876	2.023	2.895(3)	173.6(1)	4-3	**4a**

[a] Symmetry codes: (3-1) $x-1/4$, $-y+1/4$, $+z-1/4-1$; (3-2) $-x$, $-y+1/2$, $+z+1/2$; (3-3) $-x$, $-y+1/2$, $+z-1/2$; (4-1) $-x+1$, $+y-1/2$, $-z+1/2$; (4-2) x, $-y+1/2+1$, $+z-1/2$; (4-3) x, $-y+1/2$, $+z-1/2$.

by 2D experiments. For compound **3** (0.8 mg, solvent CD_3OD) the ^1H, (^1H-^{13}C) gs-HMQC, (^1H-^{13}C) gs-HMBC, ^{13}C chemical shifts were measured and assigned by 2D experiments and by comparison with **4**.

Crystal structures of compounds 3 and 4

Data collection was performed on a Nonius KappaCCD single crystal diffractometer. Images were collected at a 29 mm fixed crystal-detector distance, using the oscillation method, with 1.2° oscillation and 30 s exposure time per image. No absorption correction was applied for **3** while a semi-empirical method[28] was used for the absorption correction for **4**. The crystal structures were solved by direct methods. The refinement was performed using full-matrix least-squares on F^2. All non-H atoms were anisotropically refined. H atoms (except those of methyl groups) were located on a difference Fourier map. Selected crystal and data collection parameters are reported in Table 4 while the hydrogen-bonding parameters are collected in Table 5.†

All calculations were made at the University of Oviedo on the X-ray group computers. The following programs were used: PARST97[29] for the geometrical calculations; COLLECT (Nonius BV, 1997-2000) for data collection; HKL SCALEPACK[30] for cell refinement; HKL DENZO and SCALEPACK[30] for data reduction; SHELXS-97[31] and SHELXL97[32] for structure solution and refinement; PLATON[33] for molecular graphics and SHELXL97[32] to prepare material for publication.

Computation section: DFT and GIAO calculations

The following methods and programs have been used: B3LYP,[34] 6-31+G**,[35] 6-311++G**,[36] GIAO,[37] AIM,[38] NBO,[39] and Gaussian 98.[40] In the case of secondary interactions, the geometry of the monomers and dimers has been optimised, assuming C_s or higher symmetries, with the 6-31+G** basis set at the B3LYP computational level. The interaction energy has been corrected for the inherent basis set superposition error (BSSE) using the full counterpoise method. In order to characterise the secondary interactions, the atoms-in-molecules (AIM) and natural bond orbital (NBO) analyses have been carried out. The AIM methodology has been used to characterise the electron density of the complexes calculated. The formation of bond critical points is a necessary characteristic in HB and van der Waals interactions. In addition, the analysis of the bonding-antibonding mixing within the NBO framework allows a verification of the atoms involved in the interaction.

† CCDC reference numbers 236718 and 236719. See http://www.rsc.org/suppdata/nj/b3/b315692c/ for crystallographic data in .cif or other electronic format.

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