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REGULAR ARTICLE

The constitution of 2-hydroxypyridine in aqueous solution

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Abstract A computational strategy that replicates the kinetics of the neutral, the acetic acid-catalyzed and the 2-hydroxypyridine-catalyzed aqueous hydration of carbonyl compounds has been employed to examine the tautomeric equilibrium between 2-hydroxypyridine (H) and 2-pyridone (P) in a 2×10^{-4} M aqueous solution at 298 K. In addition to H and P, the computations have taken into account the symmetrical HH and PP dimers, the HP dimer, and mono and dihydrates of H and P. The calculated [P]/[H] equilibrium constant agrees with an experimental value obtained by measurement of ionization constants, but only if the dimers are excluded. Inclusion of the dimers lowers the calculated equilibrium constant from 862 to 70.

Keywords Tautomerism · Ab initio · SCRF · Bifunctional catalysis · DNA base pair

1 Introduction

2-Hydroxypyridine (2-HP) is the prototypical bifunctional catalyst [1]. As the hydrogen-bonded dimer with its 2-pyridone (2-PD) tautomer, 2-hydroxypyridine is also the prototypical DNA base pair analog [2–7]. Not surprisingly there is an extensive literature on the behaviour of this system in the gas-phase and non-polar media [8–13], and also in water and other polar solvents, including publications on the existence of 2-HP and 2-PD hydrates [14–17], the solvent dependence of tautomerism [18–22], and the use of ionization constants to estimate the tautomeric equilibrium constant [23–25]. It is generally agreed that 2-HP predominates in the gas-phase and non-polar media, and 2-PD predominates in water solvent.

We have recently reported on the aqueous hydration of acetone under neutral [26,27], acetic acid-catalyzed [28] and HP-catalyzed (Hsieh Y-H, Weinberg N, Wolfe S. submitted for publication) conditions. Although 2-HP is one thousand times less acidic than its isomer 3-HP, and ten million times less acidic than acetic acid, 2-HP is 600,000 times more reactive than 3-HP, 20 times more reactive than acetic acid and $k_{\mathbf{2HP}}/k_{\mathbf{neutral}} = 3.9 \times 10^7$. In each of Refs. [26–28] the experimental rate can be reproduced by a theoretical protocol which treats the aqueous hydration of a carbonyl group as a coöperative process [29,30] in which C–O bond formation and proton transfer to the carbonyl oxygen take place concurrently through a neutral bridge of solvent and (or) catalytic molecules.

The theoretical treatment of 2-HP catalysis (Hsieh et al. submitted for publication) required, inter alia, that the concentrations of all 2-HP-related species be known, and this has allowed, for the first time, a comprehensive theoretical examination of the constitution of 2-HP in aqueous solution, the subject of the present article.

This paper is dedicated to the memory of a long time friend and colleague, Fernando Bernardi.

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2 Computational details

As in our previous work [26–28], calculations were performed using Gaussian 98 [31] at the HF/3-21G level of theory [32]. The SCRF Onsager model [33–36] was used to describe water solvent with a dielectric constant of 78.5. Free energies of complexes were calculated using Eq. (1), as described in Refs. [26–28].

$$\Delta G = \Delta H - T\Delta S_{\mathrm{vib}} - 6RT \times \left[\frac{h\nu/kT}{\exp(h\nu/kT)-1} - \ln\left[1-\exp\left(\frac{-h\nu}{kT}\right)\right]\right] \quad (1)$$

The first term on the right of Eq. (1) is the enthalpy change calculated by the Gaussian programme, corrected for the basis set superposition error (BSSE) [26–28,37–48] associated with the use of the 3-21G level of theory. The second term on the right is the vibrational entropy change calculated by the Gaussian programme, and the third term on the right is a correction that takes into account the restriction of rotational and translational motions in solution [26–28]. The latter are described by a single effective frequency υ, dependent on the mass of the species.

3 Results and discussion

Table 1 collects the calculated Gibbs free energies of formation of the complexes included in our analysis. We assume that there is a dynamic thermodynamic equilibrium (Scheme 1) which involves the anhydrous tautomers 2-HP (H) and 2-PD (P), their hydrates **1a–1d**($W_1H\mu$, $\mu = 1-4$), **2a–2e**($W_2H\mu$, $\mu = 1-5$), **3a–3c**($W_1P\mu$, $\mu = 1-3$), and **4a**($W_2P\mu$, $\mu = 1$), and the dimers **5a–5c**(H_nP_m, $n+m = 2$), as well as the various constituent forms of water, W_n ($W = H_2O$, $n = 1$–4, 8).

The equilibrium constants are K_τ, K^{D}_{nm}, K^{W}_{n}, $K^{\mathrm{WH}}_{n\mu}$, and $K^{\mathrm{WP}}_{n\mu}$, and their values, derived from the respective Gibbs energies of Table 1, are listed in Table 2.

The following relationships exist among the equilibrium concentrations of these species:

$$[\mathrm{P}] = K_\tau[\mathrm{H}] \quad (2)$$

$$[\mathrm{H}_n\mathrm{P}_m] = K^{\mathrm{D}}_{nm}[\mathrm{H}]^n[\mathrm{P}]^m = (K_\tau)^m K^{\mathrm{D}}_{nm}[\mathrm{H}]^2 \quad (3)$$

$$[\mathrm{W}_n] = K^{\mathrm{W}}_{n}[\mathrm{W}_1]^n \quad (4)$$

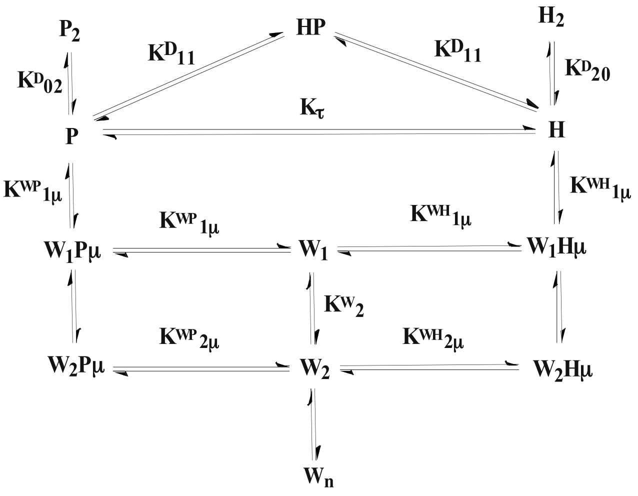
$$[\mathrm{W}_n\mathrm{H}\mu] = K^{\mathrm{WH}}_{n\mu}[\mathrm{W}_n][\mathrm{H}] = K^{\mathrm{WH}}_{n\mu}K^{\mathrm{W}}_{n}[\mathrm{H}][\mathrm{W}_1]^n \quad (5)$$

$$[\mathrm{W}_n\mathrm{P}\mu] = K^{\mathrm{WP}}_{n\mu}[\mathrm{W}_n][\mathrm{P}] = k^{\mathrm{WP}}_{n\mu}K^{\mathrm{W}}_{n}[\mathrm{P}][\mathrm{W}_1]^n = K_\tau K^{\mathrm{WP}}_{n\mu}K^{\mathrm{W}}_{n}[\mathrm{H}][\mathrm{W}_1]^n \quad (6)$$

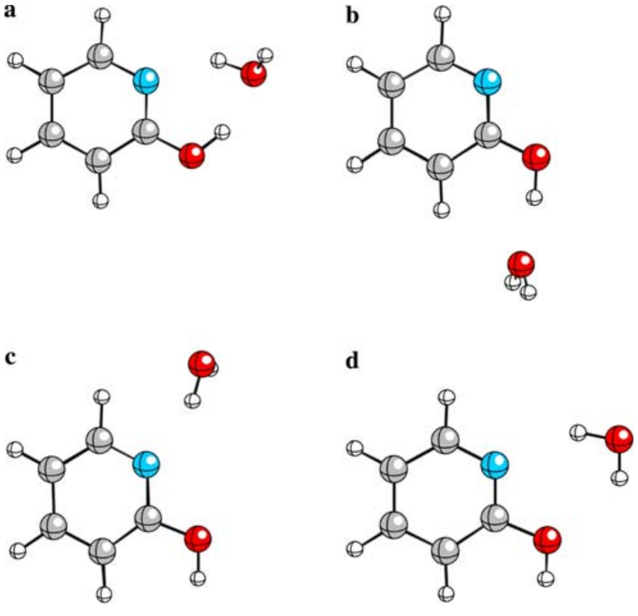
The material balance for the overall concentrations of water (C_{W}), 2-HP (C_{HP}), and 2-PD (C_{PD}) provides three additional

Table 1 Calculated Gibbs free energies of formation of the complexes of Scheme 1 in water solvent

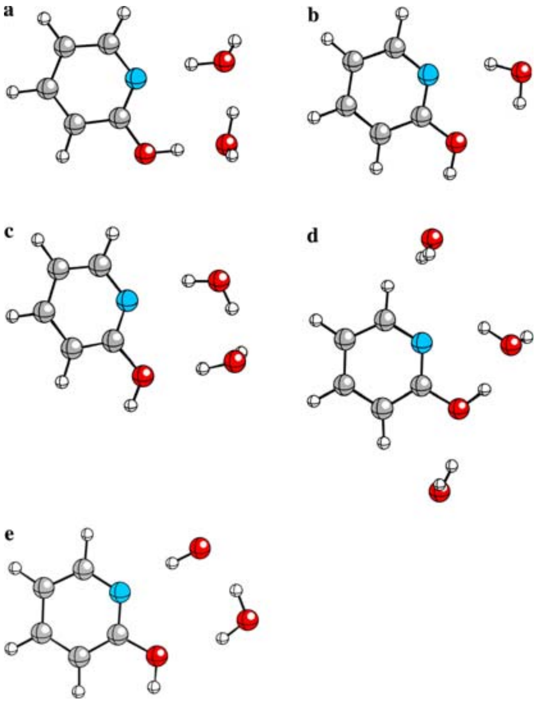
Complex	ΔG (kcal/mol)	Complex	ΔG (kcal/mol)
W_2	−3.25	W_4	−6.97
W_3	2.00	W_8	−17.21
1a	−2.21	2e	8.26
1b	−0.49	3a	3.34
1c	4.46	3b	2.48
1d	0.93	3c	3.37
2a	2.53	4a	−1.43
2b	10.61	5a	−13.00
2c	10.02	5b	−11.73
2d	15.25	5c	−10.11



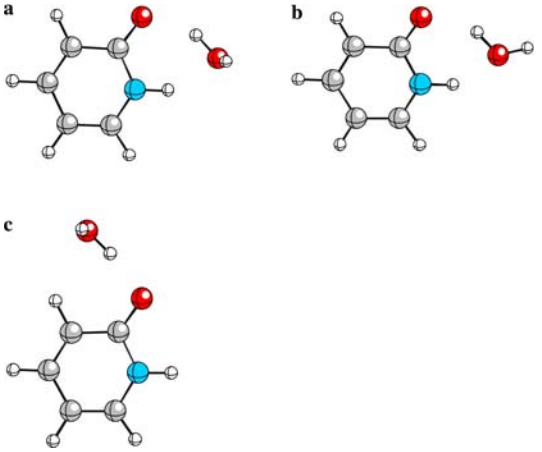
Scheme 1 Equilibrium network in the water/2-hydroxypyridine system



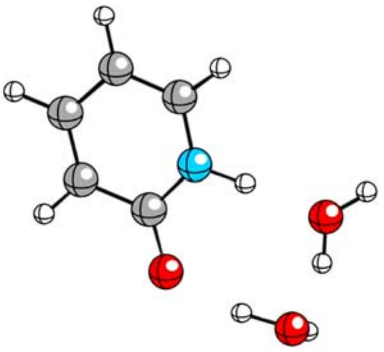
Structures 1a–d



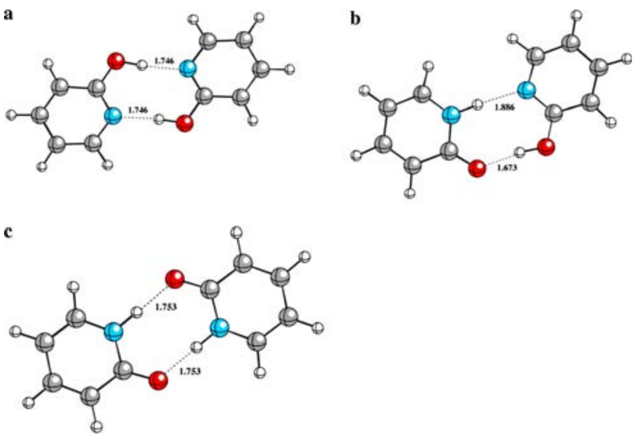
Structures 2a–e



Structures 3a–c



Structure 4a



Structures 5a–c

equations:

$$C_{\mathrm{W}} = \sum_{n} n[\mathrm{W}_n] + \sum_{n,\mu} n[\mathrm{W}_n\mathrm{H}\mu] + \sum_{n,\mu} n[\mathrm{W}_n\mathrm{P}\mu] \qquad (7)$$

$$C_{\mathrm{HP}} = [\mathrm{H}] + [\mathrm{HP}] + 2[\mathrm{H}_2] + \sum_{n,\mu} [\mathrm{W}_n\mathrm{H}\mu] \qquad (8)$$

$$C_{\mathrm{PD}} = [\mathrm{P}] + [\mathrm{HP}] + 2[\mathrm{P}_2] + \sum_{n,\mu} [\mathrm{W}_n\mathrm{P}\mu] \qquad (9)$$

Substitution of Eqs. (2)–(6) into Eqs. (7)–(9) yields the set of equations

$$\begin{aligned} C_{\mathrm{W}} &= \sum_{n} nK_n^{\mathrm{W}}[\mathrm{W}_1]^n + \sum_{n,\mu} nK_{n\mu}^{\mathrm{WH}}K_n^{\mathrm{W}}[\mathrm{H}][\mathrm{W}_1]^n \\ &\quad + \sum_{n,\mu} nK_\tau K_{n\mu}^{\mathrm{WP}}K_n^{\mathrm{W}}[\mathrm{H}][\mathrm{W}_1]^n \qquad (10) \end{aligned}$$

$$\begin{aligned} C_{\mathrm{HP}} + C_{\mathrm{PD}} &= (1+K_\tau)[\mathrm{H}] + 2\sum_{n,m}(K_\tau)^m K_{nm}^{\mathrm{D}}[\mathrm{H}]^2 \\ &\quad + \sum_{n,\mu} K_{n\mu}^{\mathrm{WH}}K_n^{\mathrm{W}}[\mathrm{H}][\mathrm{W}_1]^n \\ &\quad + \sum_{n,\mu} K_\tau K_{n\mu}^{\mathrm{WP}}K_n^{\mathrm{W}}[\mathrm{H}][\mathrm{W}_1]^n \qquad (11) \end{aligned}$$

which can be resolved to produce the unknown concentrations of water monomer, $[\mathrm{W}_1]$, and anhydrous 2-hydroxypyridine, [H]. The latter can then be substituted into Eqs. (2)–

Table 2 The calculated equilibrium constants of Scheme 1

	Constant		Constant
K_τ	5.29×10^2	$\sum K_{1\mu}^{\mathrm{PW}}$	2.21×10^{-2}
K_{20}^{D}	3.37×10^9	$\sum K_{2\mu}^{\mathrm{PW}}$	11.1
K_{02}^{D}	2.57×10^7	K_2^{W}	2.43×10^2
K_{11}^{D}	3.95×10^8	K_3^{W}	3.41×10^{-2}
$\sum K_{1\mu}^{\mathrm{HW}}$	44.2	K_4^{W}	1.29×10^5
$\sum K_{2\mu}^{\mathrm{HW}}$	1.40×10^{-2}	K_8^{W}	4.08×10^{12}

Table 3 Calculated concentrations of the species present at 298 K in a 2.00×10^{-4} M solution of 2-hydroxypyridine

Species	Concentration (M)	Percent of 55.5 M	Percent of 2.00×10^{-4}M
W_1	3.37×10^{-2}	0.06	
W_2	2.75×10^{-1}	0.99	
W_3	1.31×10^{-6}	0.00	
W_4	1.66×10^{-1}	1.20	
W_8	6.78	97.75	
H monomer	3.61×10^{-9}		0.00
P monomer	1.91×10^{-6}		0.95
H_2 dimer	4.38×10^{-8}		0.04
P_2 dimer	9.34×10^{-5}		93.36
H_1P_1 dimer	2.72×10^{-6}		2.72
$W_1H = \sum W_1H\mu$	5.37×10^{-9}		0.01
$W_2H = \sum W_2H\mu$	1.39×10^{-11}		0.00
$W_1P = \sum W_1P\mu$	1.42×10^{-9}		0.00
$W_2P = \sum W_2P\mu$	5.85×10^{-6}		2.92

(6) to obtain the concentrations of all other species, and into Eqs. (8), (9) and (12) to obtain the theoretical value of the tautomeric equilibrium constant.

$$K_{\mathrm{calc}} = \frac{C_{\mathrm{PD}}}{C_{\mathrm{HP}}} \tag{12}$$

Table 3 summarizes the calculated concentrations of the species and the percentages of these species at 298 K in a 2×10^{-4} M aqueous solution of 2-hydroxypyridine ($C_{\mathrm{HP}} + C_{\mathrm{PD}} = 2 \times 10^{-4}$ M; $C_{\mathrm{W}} = 55.5$ M).

As in previous work [26,27], our computational treatment reproduces Benson's cyclic tetramer–cubic octamer two-structure model of liquid water [49]. From Table 3, $K_t = 529$ for the anhydrous tautomers at 298 K, corresponding to a free energy difference of 3.71 kcal/mol. Inclusion of the hydrates gives

$$\begin{aligned}[2\mathrm{HP}] &= 3.61 \times 10^{-9} + 5.37 \times 10^{-9} \\ &\quad + 1.39 \times 10^{-11} = 8.99 \times 10^{-9} \\ [2\mathrm{PD}] &= 1.91 \times 10^{-6} + 1.42 \times 10^{-9} \\ &\quad + 5.85 \times 10^{-6} = 7.76 \times 10^{-6}\end{aligned}$$

and $K_t = 862$, corresponding to a free energy difference of 4.00 kcal/mol. Although this number is in almost perfect agreement with the reported [23–25] experimental value ($\Delta G = 3.97$ kcal/mol at 20^{circ}C), *it does not include the dimers which, collectively, comprise 96% of the total*. When these are taken into account we have

$$\begin{aligned}[2\mathrm{HP}] &= [\mathrm{H}] + 2[\mathrm{HH}] + [\mathrm{HP}] + [\mathrm{W_1H}] \\ &\quad + [\mathrm{W_2H}] = 2.86 \times 10^{-6} \\ [2\mathrm{PD}] &= [\mathrm{P}] + 2[\mathrm{PP}] + [\mathrm{HP}] + [\mathrm{W_1P}] \\ &\quad + [\mathrm{W_2P}] = 1.97 \times 10^{-4}\end{aligned}$$

and $K_t = 70.0$. The principal monomeric species is the dihydrate **4a**.

The experimental value for the tautomeric equilibrium was obtained from spectrophotometric measurements of ionization constants. We do not know whether such measurements can take dimers into account, and must, therefore, conclude that an experimental reexamination of the constitution of 2-hydroxypyridine in aqueous solution is desirable.

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References

1. Swain CG, Brown JF Jr (1952) J Am Chem Soc 74:2538
2. Chou P-T, Wei C-Y, Hung F-T (1997) J Phys Chem B 101:9119
3. Müller A, Talbot F, Leutwyler S (2001) J Chem Phys 115:5192
4. Roscioli JB, Pratt DW (2003) PNAS 100:13752
5. Meuwly M, Müller A, Leutwyler S (2003) PCCP 5:2663
6. Thanopulos I, Shapiro M (2005) J Am Chem Soc 127:14434
7. Frey JA, Leist R, Leutwyler S (2006) J Phys Chem A 110:4188
8. Rony PR, McCormack WE, Wunderly SW (1969) J Am Chem Soc 91:4244
9. Rony PR (1969) J Am Chem Soc 91:6090
10. Rony PR, Neff RO (1973) J Am Chem Soc 95:2896
11. Lee Y-N, Schmir GL (1979) J Am Chem Soc 101:3026 and references cited therein

12. Engdahl K-A, Bivehed H, Ahlberg P, Saunders WH Jr (1983) J Am Chem Soc 105:4767
13. Morpurgo S, Bossa M (2003) PCCP 5:1181
14. Bensaude O, Chevrier M, Dubois J-E (1979) J Am Chem Soc 101:2423
15. Beak P, Covington JB, White JM (1980) J Org Chem 45:1347
16. Held A, Pratt DW (1993) J Am Chem Soc 115:9708
17. Matsuda Y, Ebata T, Mikami N (1999) J Chem Phys 110:8397
18. Beak P, Fry FS, Lee J, Steele F (1976) J Am Chem Soc 98:171
19. Beak P (1977) Acc Chem Res 10:186, and references cited therein
20. Brown RS, Tse A, Vederas JC (1980) J Am Chem Soc 102:1174
21. Matsuda Y, Ebata T, Mikami N (2000) J Chem Phys 113:573
22. Matsuda Y, Ebata T, Mikami N (2001) J Phys Chem A 105:3475
23. Albert A, Phillips JN (1956) J Chem Soc 1294
24. Mason SF (1958) J Chem Soc 674
25. Beak P, Lee JT Jr (1969) J Org Chem 34:2125
26. Wolfe S, Kim C-K, Yang K, Weinberg N, Shi Z (1995) J Am Chem Soc 117:4240
27. Wolfe S, Shi Z, Yang K, Ro S, Weinberg N, Kim C-K (1998) Can J Chem 76:114
28. Hsieh Y-H, Weinberg N, Yang K, Kim C-K, Shi Z, Wolfe S (2005) Can J Chem 83:769
29. Eigen M (1965) Discuss Faraday Soc 39:7
30. Huang HH, Robinson RR, Long FA (1966) J Am Chem Soc 88:1866
31. Frisch MJ et al (1998) Gaussian 98, Revision A.6. Gaussian, Inc, Pittsburgh
32. Hehre WJ, Radom L, Schleyer PvR, Pople JA (1986) Ab initio molecular orbital theory. Wiley, New York
33. Wong MW, Frisch MJ, Wiberg KB (1991) J Am Chem Soc 113:4776
34. Wong MW, Wiberg KB, Frisch MJ (1991) J Chem Phys 95:8991
35. Wong MW, Wiberg KB, Frisch MJ (1992) J Am Chem Soc 114:523
36. Wong MW, Wiberg KB, Frisch MJ (1992) J Am Chem Soc 114:1645
37. Boys SF, Bernardi F (1970) Mol Phys 19:553
38. Ventura ON, Coitiño EL, Irving KA, Iglesias A, Lledós A (1990) J Mol Struct (Theochem) 210:427
39. Cook DB, Sordo TL, Sordo JA (1990) J Chem Soc Chem Comm 185
40. Åstrand PO, Wallqvist A, Karlström GJ (1991) J Phys Chem 95:6395
41. Eggenberger R, Gerber S, Huber H, Searles D (1991) Phys Lett 183:223
42. Valiron P, Vibók A, Mayer I (1993) J Comp Chem 14:401
43. Turi L, Dannenberg JJ (1993) J Phys Chem 97:2488
44. Dobado JA, Molina JM (1993) J Phys Chem 97:7499
45. Davidson ER, Chakravorty SJ (1993) Chem Phys Lett 217:48
46. Mayer I, Vibók A, Valiron P (1994) Chem Phys Lett 230:35
47. Neuheuser T, Hess BA, Reutel C, Weber E (1994) J Phys Chem 98:6459
48. Kieninger M, Suhai S, Mayer I (1994) Chem Phys Lett 230:485
49. Benson SW, Siebert ED (1992) J Am Chem Soc 114:4269