On the tautomerization reaction 2-pyridone⇌2-hydroxypyridine: an ab initio study

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The reaction 2-pyridone (PY) ⇌ 2-hydroxypyridine (HP) has been studied as a prototype of tautomerism of heteroaromatic compounds. Geometrical structures and relative energies of the two tautomers as well as of the transition state (TS) for the intramolecular hydrogen transfer have been obtained using ab initio methods with different basis sets. Correlation energy is introduced through configuration interaction within a double-zeta basis set plus polarization functions. Analytical second derivatives are also calculated to obtain the harmonic frequencies.

1. Introduction

The protomeric tautomerism of heteroaromatic compounds involving the transfer of a hydrogen between a cyclic nitrogen and a substituent atom directly adjacent to the ring has been a field of much interest in experimental as well as theoretical chemistry [1], given that these reactions are thought to be of importance in biological processes such as mutagenesis [2–4]. The simplest model for nucleic acid bases tautomerism is the system 2-pyridone/2-hydroxypyridine:
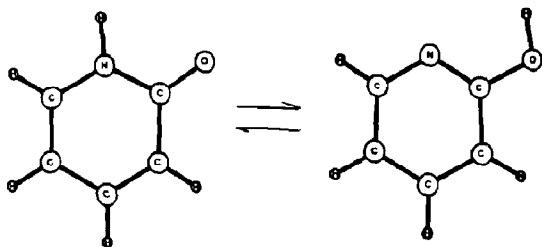
Scheme 1.

This reaction has been studied by means of different spectroscopic techniques [5–12]. From a theoretical

point of view, there has also been a large amount of work dealing with this reaction. Ab initio results [13–18] offer a wide range for the energy of the lactim form (HP) relative to the lactam (PY) that varies from +2.06 to −3.46 kcal/mol, thus reversing the stability pattern.

Some general limitations of the previous works may be noted: first, though the basis set reaches quite a high level (6-31G**), the geometry is always taken from a lower basis set (6-31G* at its best), thus neglecting p polarization functions on hydrogens. On the other hand, correlation energy is introduced within the second-order Møller–Plesset perturbation theory (MP2) or using a coupled-cluster method (CC). As both methods are non-variational, the results could be misleading. Furthermore, the transition state (TS) for the intramolecular reaction has only been located at STO-3G and 3-21G levels of calculation.

In this paper we present the results of the highest level ab initio calculations that have been carried out up to now on this reaction in order to study the energetics, the geometries and the vibrational frequencies of the two minima and the transition state. Correlation energy is also introduced through a variational configuration interaction scheme (CI).

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2. Methodology

The geometries of the three stationary points were fully optimized by the energy-gradient method without any constraint on the geometrical parameters. The basis sets used were minimum (STO-3G) [19] and double-zeta plus polarization d functions in the heavy atoms (DZP1) and also including a set of p functions on hydrogens (DZP2). The double-zeta basis set is that of Huzinaga and Dunning [20,21] which consists of (9s5p/4s2p) on heavy atoms and (4s/2s) on hydrogens. The polarization-function exponents were $\alpha_{d(C)}=0.75$, $\alpha_{d(O)}=0.85$, $\alpha_{d(N)}=0.8$ and $\alpha_{p(H)}=0.75$. Configuration interaction (CI) was performed including all single and double excitations (CISD). A frozen-core approximation was used to prevent electronic excitations from inner-shell orbitals.

All quadratic force constants and the resulting harmonic vibrational frequencies were determined with use of analytic SCF second-derivative techniques [22,23]. Thermodynamic quantities and the zero-point energy (ZPE) were computed using the statistical thermodynamic formulae within the ideal gas, rigid rotor and harmonic oscillator approximations [24]. As usual [25], we expect the theoretical SCF frequencies to be higher than the experimental ones by a factor of 10–15%. Therefore, the frequencies presented in this paper have been multiplied by a factor of 0.87.

3. Results and discussion

3.1. Geometrical structures

The geometries obtained at the best basis set used (DZP2) for the two tautomeric minima as well as for the transition state are presented in table 1. The three structures are planar. Fig. 1a pictures the numbering used in the table.

A recent work [12] claims that the electronic spectra in the gas phase indicates that PY has a non-planar form in its ground singlet state. Our results do not support this idea, an analysis of second derivatives of the energy having shown that the planar structure found here for the PY is a true minimum of the whole potential-energy hypersurface (all the

Table 1
Geometries obtained at the DZP2 level of calculation for the pyridone, hydroxypyridine and the transition state for the intramolecular hydrogen transfer. Bond lengths are in Å and bond angles in deg. For numeration see fig. 1a

Parameter	PY	TS	HP
1–3	1.38	1.34	1.31
3–4	1.46	1.41	1.40
4–5	1.35	1.37	1.38
5–6	1.44	1.42	1.40
6–7	1.34	1.37	1.38
7–1	1.37	1.33	1.33
2–3	1.21	1.27	1.34
1–8	1.00	1.33	–
2–8	–	1.27	0.95
∠1–3–4	113.9	120.8	124.1
∠3–4–5	121.0	115.9	117.3
∠4–5–6	121.4	122.2	119.7
∠5–6–7	117.6	118.0	117.4
∠6–7–1	121.2	119.8	123.7
∠7–1–3	125.0	123.3	117.9
∠1–3–2	120.5	104.9	117.7

eigenvalues of the force constant matrix are positive).

Comparison of geometries for the three stationary points shows, as expected, that the transition-state bond lengths are intermediate between the values of the two minima but this is not the case for the angles. That is, in the transition state the angle between the three heavy atoms involved in the H-atom transfer (∠1–3–2 in table 1) clearly diminishes in order to allow the hydrogen to be transferred through a four-membered ring (see fig. 1). These geometrical changes are responsible for the high energetic barrier obtained here as compared with other hydrogen transfers where a five- or more-membered ring is involved.

3.2. Energetics

Table 2 presents the results obtained at different levels of calculation. The "best estimate" results refer to the values obtained by adding the CISD correction energy to the best SCF results obtained within the DZP2 basis set, the ZPE correction being also included.

Because of the very small difference between the two tautomers, the relative energy changes its sign through the table. Our results show globally the same
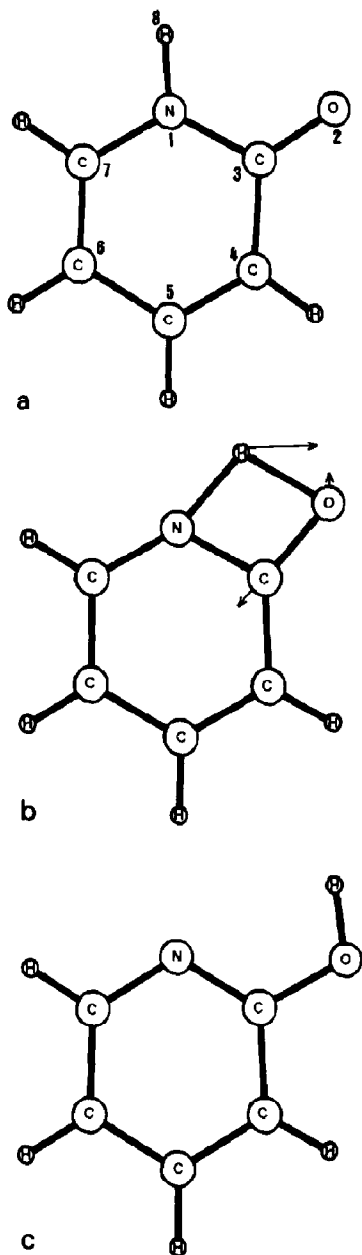
a

b

c

Fig. 1. Geometrical structures of the three stationary points involved in the considered tautomeric reaction. (a) 2-Pyridone (PY). (b) Transition state (TS). (c) 2-Hydroxypyridine (HP). In (b) arrows indicate the direction of the transition vector.

Table 2
Energetics (values in kcal/mol) for the pyridone–hydroxypyridine tautomerization reaction

Basis/method [a]	Pyridone	TS	Hydroxy-pyridine
STO-3G//STO-3G	0	50.65	−15.42
DZP1//STO-3G	0	51.09	0.093
DZP1//DZP1	0	51.91	−0.44
DZP1//DZP2	0	51.91	−0.42
DZP2//DZP2	0	49.92	−1.51
CISD(DZP1)//DZP1	0	43.46	0.068
best estimate [b]	0	38.45	−1.12
H [c]	0	38.09	−1.16
G [c]	0	38.77	−0.96

[a] // means "at the geometry of".

[b] Including zero-point energy corrections.

[c] $T = 405.15$ K.

icance. On the other hand, we note that the CI calculations stabilize the PY isomer, this behavior being opposite to the trends observed when correlation energy was introduced within perturbative [13] and coupled-cluster [18] methods.

Experimentally [6], the relative binding energy between the two isomers is -0.3 ± 2.5 kcal/mol. Our best estimation of -1.1 kcal/mol is one of the best approximations to the experimental measure.

For the transition state, the comparison of methods show more important differences. The introduction of correlation lowers the barrier by about 10% from the SCF barrier. ZPE corrections also reduce the effective barrier so that the best estimated value is the lowest one. However, the final value of 38.4 kcal/mol is still high enough to rule out an intramolecular hydrogen-transfer mechanism.

Finally, the thermodynamic quantities were also evaluated at the highest SCF level (DZP2) at 405.15 K. The relative enthalpy (H) and free enthalpy (G) values are listed in the two last rows of table 2. These values have been obtained by adding the CI correction to the SCF (DZP2) thermodynamic results. This fact can be justified given that the real thermodynamic corrections at the CI level are expected to be very similar since only the (small) harmonic vibrational terms would be modified due to the change in the curvature of the potential energy hypersurface.

Experimentally [6,7,9,10,26] the standard relative enthalpy H of the HP ranges from 0.7 to −0.8 kcal/mol, whereas for the free enthalpy G, the limits

trends observed in previous calculations: minimal basis sets favor the lactam isomer (PY) whereas polarization functions stabilize the lactim form (HP). Consequently, the introduction of p polarization functions on hydrogens seems to be of great signif-

are -0.58 and -0.89 kcal/mol. Our theoretical values lie slightly below these limits.

3.3. Vibrational frequencies and IR spectra

The vibrational frequencies and their respective intensities have been evaluated at the SCF (DZP2) level of calculation so the theoretical IR spectra of the three stationary points are obtained. However, as the IR spectra have not been unraveled experimentally, we will limit this study to the frequencies that can be used to differentiate between both tautomers. This point is important as the relative intensity of the bands can be used to determine experimentally the PY/HP concentration ratio and – assuming a Boltzmann distribution – the energy difference between both tautomers.

With this approach, there are two frequencies that should be clearly different in both molecules and sufficiently intense to allow this kind of measurement: The first one is the highest frequency that changes from 3376.5 cm^{-1} with an intensity of 95.3 km/mol in the PY (N–H stretch) to 3625.6 cm^{-1} and 141.5 km/mol in the HP (O–H stretch). The second frequency is the C=O stretch in the PY which is the more intense line (945.3 km/mol). Its frequency of 1683.5 cm^{-1} is the highest between the heavy atom-heavy atom stretches and so it should present a clearly differentiated line in the IR spectra. This last frequency is the only one suggested in the previous 3-21G calculation [18] to be used in order to estimate the PY/HP concentration ratio.

We finally note that our DZP2 results differ from the 3-21G ones recently reported [18]. Though qualitatively both results show similar trends, it has been seen that frequencies as well as intensities present significant differences. This fact clearly demonstrates that vibrational frequencies are very sensitive to the shape of the potential-energy surface near the stationary point.

4. Conclusions

We summarize the following points from the present work: As was previously reported [13], the optimized geometry of the two tautomers shows only slight differences when changing the basis set. However, since the relative energy of the two molecules is very small, the use of different geometries may reverse the stability pattern. We suggest that the best thing to do is to optimize the geometries at any considered level of calculation. Thus, it would be desirable to optimize the geometry including energy correlation but this calculation is, up to now, beyond present computer capabilities.

At our best level of calculation, we obtain that the energy of the hydroxypyridine relative to the pyridone is -1.1 kcal/mol. This result agrees with the experimental estimation of -0.3 ± 2.5 kcal/mol though more accurate experimental data would be desirable. The stretching of the transferring hydrogen is the highest frequency in the two minima. This normal mode and the C=O stretching in the PY are the best-suited frequencies to elucidate the IR spectra in the gas phase and to estimate the tautomeric equilibrium constant.

The transition-state geometry for the intramolecular hydrogen transference has a strained four-membered ring so that the hydrogen can be transferred. Thus, a high energy barrier is found even at a CI level, ruling out the possibility of a classical intramolecular tautomerism. However, a direct H-atom transfer is still feasible through a tunneling mechanism. The high value of the imaginary frequency at the TS (2039.1i cm^{-1}) supports the need for additional work on this subject.

References

[1] J.S. Kwiatkowski, T.J. Zielinski and R. Rein, Advan. Quantum Chem. 18 (1986) 85.

[2] M.D. Topal and J.R. Fresco, Nature 263 (1976) 285, 289.

[3] W.G. Cooper, Intern. J. Quantum Chem. 14 (1978) 71.

[4] R. Rein and M. Shibata, in: Nucleic acids: the vectors of life, eds. B. Pullman and J. Jortner (Reidel, Dordrecht, 1983) p. 479.

[5] P. Beak and F.S. Fry Jr., J. Am. Chem. Soc. 95 (1973) 1700.

[6] P. Beak, F.S. Fry Jr., J. Lee and F. Steele, J. Am. Chem. Soc. 98 (1976) 171.

[7] P. Beak, Accounts Chem. Res. 10 (1977) 186.

[8] M.J. Nowak, K. Sczepaniak, A. Barski and D. Shugar, Z. Naturforsch. 33C (1978) 876.

[9] D.H. Aue, L.D. Betowski, W.R. Davidson, M.T. Bowers, P. Beak and J. Lee, J. Am. Chem. Soc. 101 (1979) 1361.

[10] R.S. Brown, A. Tse and J.C. Vederas, J. Am. Chem. Soc. 102 (1980) 1174.

[11] M. Kuzuya, A. Noguchi and T. Okuda, J. Chem. Soc. Perkin Trans. II (1985) 1423.

[12] M.R. Nimlos, D.F. Kelley and E.R. Bernstein, J. Phys. Chem. 93 (1989) 643.

[13] H.B. Schlegel, P. Gund and E.M. Fluder, J. Am. Chem. Soc. 104 (1982) 5347.

[14] M.J. Scanlan, I.H. Hillier and A.A. McDowell, J. Am. Chem. Soc. 105 (1983) 3568.

[15] M.J. Scanlan and I.H. Hillier, Chem. Phys. Letters 107 (1984) 330.

[16] P. Cieplak, P. Bash, U. Chandra Singh and P.A. Kollman, J. Am. Chem. Soc. 109 (1987) 6283.

[17] J.S. Kwiatkowski, R.J. Bartlett and W.B. Person, J. Am. Chem. Soc. 110 (1988) 2353.

[18] L. Adamowicz, Chem. Phys. Letters 161 (1989) 73.

[19] W.J. Hehre, R.F. Stewart and J.A. Pople, J. Chem. Phys. 51 (1969) 2657.

[20] S. Huzinaga, J. Chem. Phys. 42 (1965) 1293.

[21] T.H. Dunning, J. Chem. Phys. 53 (1970) 2823.

[22] P. Saxe, Y. Yamaguchi and H.F. Schaefer III, J. Chem. Phys. 77 (1982) 5647.

[23] Y. Osamura, Y. Yamaguchi, P. Saxe, D.J. Fox, M.A. Vincent and H.F. Schaefer III, J. Mol. Struct. 103 (1983) 183.

[24] D.A. McQuarrie, Statistical mechanics (Harper and Row, New York, 1976) pp. 129–141.

[25] W.J. Hehre, L. Radom, P. von R. Schleyer and J.A. Pople, Ab initio molecular orbital theory (Wiley, New York, 1986) pp. 229–261.

[26] C. Guimon, G. Garralbe and G. Pfister-Guilouzo, Tetrahedron Letters (1979) 2585.