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Intramolecular proton transfer in tautomeric 2-Imidazolone and 2-thioimidazolone

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ABSTRACT: The enol ⇌ keto and thiol ⇌ thione prototropic tautomerisms in 2-imidazolone and 2-thioimidazolone were studied by *ab initio* methods in the frame of MO theory. The energetics of these reactions were derived using various basis sets and levels including both polarization and diffuse functions. To account for electron correlation, second-, third- and fourth-order Møller–Plesset perturbation theory was applied. The thermodynamics for both reactions indicate that the keto and thione are the predominant species in the gas phase, whereas in solution the enol and keto forms are present in comparable concentrations. For both tautomerization reactions the transition states for the intramolecular mechanism were found and fully characterized. The calculated energetic barrier for the enol–keto system is 41.6 kcal mol^{-1}, whereas that for the thiol–thione system is 32.5 kcal mol^{-1} (1 kcal = 4.184 kJ). The study of the solvent effect, using the PCM model, on E_a reveals that solvents lower the barrier by ca 11 and 7 kcal mol^{-1} for the enol–keto and thiol–thione systems, respectively. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: intramolecular proton transfer; tautomerism; 2-imidazolone; 2-thioimidazolone; MO theory

INTRODUCTION

The proton transfer reaction is one of the simplest and most important reactions in chemistry and biology.[1–13] In general, biological systems are so complex that they are not computationally accessible to be simulated at high levels of theory. Accordingly, one is forced to simplify the problem and hence to work on the 'active' part of the molecule only. 2-Imidazolone (IZ) in its enolic form would be the active part of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG), an intermediate in the oxidative stress of guanine (G), and considered as the most biologically relevant G damage in oxidized genomic DNA, although Vialas *et al.*[14] found that the artificial Mn–TMPyP/$KHSO_5$ nuclease can oxidize dG to a 4-imidazolone nucleoside within 1 min without 8-oxo-dG being involved. In 8-oxo-G, the aglycone moiety of 8-oxo-dG, the imidazole ring of the purine has been oxidized at C-8 to yield a hydroxyimidazole derivative fused to the 2-amino-6-oxopyrimidine ring.[15–18] Using transition-state calculations, Mishra and Mishra[19] showed that tautomerism of G where tautomeric forms co-exist would be facilitated by the presence of H^+ and OH^- fragments coming from water and that the co-existence of both tautomers 'appears to make C-8 carbon atoms' susceptible to attack by OH^- fragments, and hence a good explanation is given for the formation of 8-oxo-dG which 'serves as a biomarker for the oxidative damage to DNA.' If one considers the hydroxyimidazole ring only (C-8 becomes C-2), its prototropic tautomerism (enol–keto) can theoretically be studied at high levels by *ab initio* methods. As a part of our continued interest in the electronic structure of small bioactive molecules, in this work we studied the enol–keto interconversion reaction in IZ. The study of the prototropic tautomerism in IZ is important since if the enol form is present at an appreciable concentration, the 8-oxo-dG intermediate and the oxidative stress attack at the C-8 atom of deoxyguanine will be both experimentally and theoretically supported. The thiol–thione tautomerism in 2-thioimidazolone (TIZ) was also studied to compare the effect of replacing oxygen by sulfur on the thermodynamics of both molecular systems. TIZ has been suggested as a chemical precursor of some oxo compounds found in a group of marine alkaloids such as aplysinopsin and polyandrocarpine.[20] The results show that the keto and thione species are predominant in IZ and TIZ, respectively, in the gas phase. In solution, the enol tautomeric form is present at ca 50%, whereas the thiol form remains constant at ca 4%. For both molecular systems the intramolecular proton transfer mechanisms were elucidated and the corresponding activation energies calculated.

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COMPUTATIONAL METHODS

Geometry optimizations for all species studied were carried out at the HF/6–31G** and MP2/6–31G** levels using the Gaussian 98 series of programs.[21] The initial geometries were those found for imidazole[22] and 1-*p*-chlorophenyl-4-(α-D-erythrofuranosyl)-4-imidazolone-2-thione.[23] Comparing the energies calculated at the MP2/6–31G**//HF/6–31G** and MP2/6–31G**//MP2/6–31G** levels for the enol–keto and thiol–thione molecular systems, we found that the energy difference in IZ is ca 0.004 kcal mol^{-1}, whereas in TIZ it is 0.016 kcal mol^{-1} (1 kcal = 4.184 kJ). Accordingly, it seems clear that optimization at the correlated level is not necessary to obtain accurate energies. In addition, the difference in the calculated bond lengths are just ca 0.04 Å, whereas the bond angle variation on going from the HF/6–31G** to the MP2/6–31G** level is ca 1.02° for both molecular systems. Frequency and IR intensities predicted at the equilibrium geometries (HF/6–31G**) produce all real values and hence all four structures are local minima. Energy calculations were performed using various basis sets to determine the optimum level to be employed and to determine the effect of including both polarization and diffuse functions. In all cases electron correlation at the second-, third- and fourth-order Møller–Plesset theory in the frozen approximation were used. The QCISD was also explored, although our limited computer facilities did not allow us to include triple (T) and quadruple (Q) substitutions. The calculated energies were corrected for zero point vibrational energies (ZPE) and the enthalpy and free energy changes for the tautomerization reactions were derived from the sums of the electronic and thermal enthalpies and free energies, respectively. The transition states (TSs) for both reactions were located using the synchronous transit-guided quasi-Newton (STQN) method[24,25] implemented in the Gaussian 98 package.[21] STQN uses a quadratic synchronous transit approach to approach close to the quadratic region of TS. The TSs were further optimized by quasi-Newton or eigenvector-following algorithms.[26] The TSs were characterized as described elsewhere.[27] In fact, frequency calculations produced just one imaginary frequency for each TS. The imaginary frequencies were 2359i and 2140i cm^{-1} for IZ and TIZ, respectively. These high frequencies indicate that the potential energy barriers are very narrow. Animation of the imaginary vibrational modes using either Gaussview[28] or Gopenmol[29] clearly showed that they lead to the reactants (enol or thiol forms) and the products (keto or thione). In addition, the TS → enol (or thiol) and TS → keto (or thione) reaction paths were followed using the IRC (intrinsic reaction coordinate) procedure. The calculated TSs for the enol ⇌ keto and thiol ⇌ thione reactions connect the corresponding TS with the reactants and products and hence we can conclude that real TSs were found.

To estimate the solute–solvent interactions, we applied the PCM (polarized continuum method)[30–35] after testing its capability to reproduce the solvation free energies of more than 40 neutral molecules in different solvents. Although the method behaved well in most cases studied, it failed to reproduce the experimental data in a number of cases. This was particularly true when a solvent other than water was used. PCM as modified by Wiberg and coworkers,[36,37] known as IPCM (isodensity polarized continuum method), did not perform well in reproducing the experimental data. The free energies of solvation derived from PCM calculations contain the electrostatic and the non-electrostatic terms (cavitation, dispersion and repulsion energies). Since the structural parameters change very little on going from the from the gas phase to solution and therefore no large effect on solvation free energies is to be expected, the gas-phase geometries were used in applying the PCM method. In fact, this assumption has been proved to be acceptable in many cases.[27,38] In the present study, geometry optimization at the HF/6–31G** level in DMSO using Onsager's SCRF method showed that the largest variations in bond distances and angles are ca 0.07 Å and 0.39°, respectively.[19,27] The free energies in solution ($G°_{soln}$) were calculated from $G°_{soln}$ equals; $\Delta G°_{gas} + \Delta G°_{s}$, where $\Delta G°_{s}$ is the free energy of solvation. The concentrations for each species were approximately estimated from the corresponding $\Delta G°$ values. The solvents in the present work were isooctane ($\epsilon = 1.90$), CCl_4 ($\epsilon = 2.23$), chloroform ($\epsilon = 4.90$), THF ($\epsilon = 7.58$), CH_2Cl_2 ($\epsilon = 8.93$), octanol ($\epsilon = 10.34$), ethanol ($\epsilon = 24.55$), dimethy sulfoxide (DMSO) ($\epsilon = 46.70$) and H_2O ($\epsilon = 78.39$).

RESULTS AND DISCUSSION

Molecular structures

IZ and TIZ are each capable of existing in two tautomeric forms: IZ can exist as the enol and keto and TIZ as the thiol and thione tautomers. Figure 1 shows the optimized geometries for these tautomers. The atom numbering used in Table 1 is also given in Fig.1. Table 1 shows that for all four tautomeric species the torsional angles are either 0 or 180° and accordingly all possess planar structures. The enol and thiol rings possess a single and a double C—N bond and in the keto and thione forms both distances are ca 1.37 Å, i.e. a typical single C—N bond in five-membered rings. The C-4—C-5 bond is double-bond in character with values lying within the range 1.32–1.34 Å. The internal bond angles show an interesting trend on going from enol (or thiol) to keto (or thione). Comparing the structural parameters given in Tables 1 and 2, it can be inferred that the N-1—C-2—N-3 angles increase by ca 10° in the enol and thiol species with the corresponding decrease in the C-2—N-3—C-4 angles by the same amount. In keeping with these variations, the N-3—C-4—C-5 angles decrease by ca 4° yielding bond distances

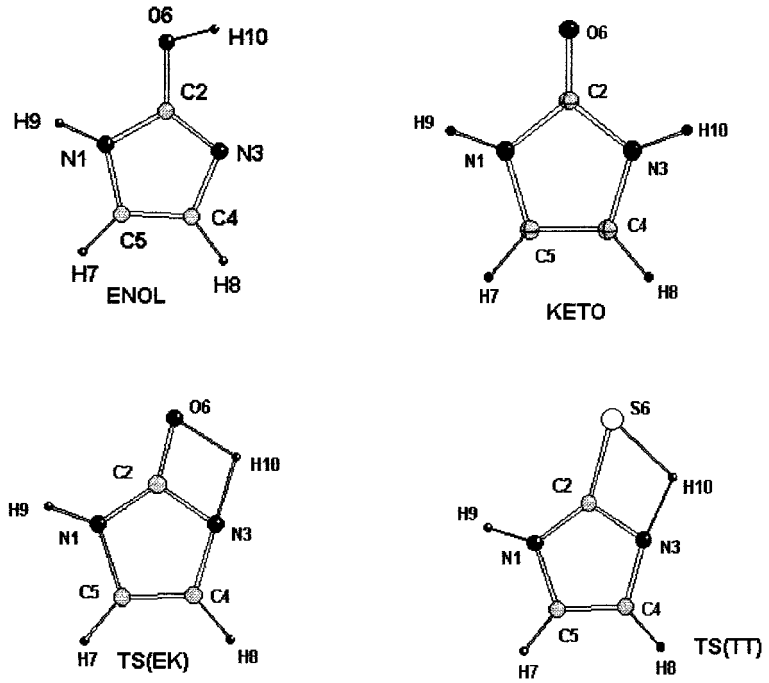

Figure 1. Optimized structures and atom numbering for the tautomeric forms of IZ and its TS(EK). The TS(TT) is also shown

longer in the enol (1.343 Å) and thiol (1.346 Å) compared with the keto (1.327 Å) and thione (1.331 Å). These structural effects lead to compressed enol and thiol forms (C_s symmetry) with respect to the C_{2v} symmetric keto and thione species. The exocyclic bond distances and angles are in good agreement with the experimental values.[39–41]

The enol–keto and thiol–thione TSs are also planar since the dihedral angles do not change more than 0.06°. The enol–keto TS [TS(EK)] and thiol–thione TS [TS(TT)] resemble the enol (or thiol) tautomer in its bond distances except for C-2—O-6 (and C-2—S-6), which is in between the two tautomeric forms. In both TS(EK) and TS(TT), H-10 bridges N-3 and O-6 or S-6, respectively. In TS(EK) the bridge is slightly asymmetric since a difference of ca 0.06 Å between the N-3···H-10 and O-6···H-10 non-bonded distances is found. On the

Table 1. Optimized bond lengths and angles for the enol–keto and thiol–thione tautomers of IZ and TIZ and their transition states at the HF/6–31G** level

	Enol	TS	Keto	Thiol	TS	Thione
Bond distances (Å)						
N1—C2	1.340	1.331	1.368	1.348	1.328	1.344
C2—N3	1.283	1.308	1.368	1.287	1.307	1.344
N3—C4	1.382	1.383	1.393	1.376	1.379	1.387
C4—C5	1.343	1.341	1.327	1.346	1.344	1.331
C2—06/S6	1.328	1.267	1.202	1.764	1.735	1.683
C5—H7	1.068	1.068	1.068	1.068	1.068	1.068
C4—H8	1.070	1.068	1.068	1.070	1.068	1.068
N1—H9	0.992	0.992	0..991	0.992	0.992	0.993
N3···H10		1.295	0.991		1.358	0.993
O6 (S6)···H10	0.945	1.354		1.324	1.681	
Bond angles (°)[a]						
N1C2N3	113.7	111.4	103.8	112.5	110.6	104.5
C2N3C4	104.4	107.6	110.8	105.2	107.7	111.1
N3C4C5	110.8	108.0	107.3	110.5	108.0	106.6
N1C206(S6)	119.6	138.7	128.1	121.3	141.2	127.8
N1C5H7	122.3	121.7	122.4	122.3	122.0	122.5
N3C4H8	121.1	123.3	122.4	121.2	122.9	122.5
C2N1H9	125.7	126.3	122.0	126.6	125.8	121.8
C2O6(S6)H10	108.1	72.0		94.8	61.3	

[a] All dihedral angles are either 0.0 or 180.0°.

Table 2. Energetics and dipole moments for the enol, keto, thiol and thione tautomeric forms and their TS

Energy[a]	Enol	TS	Keto	Thiol	TS	Thione
HF/6–31G**	−299.696243	−299.604162	−299.711511	−622.334825	−622.264422	−622.355142
MP2/6–31G**	−300.490602	−300.519899	−300.603272	−623.182605	−623.129957	−623.195715
MP3/6–31G**	−300.606641	−300.527946	−300.618783	−623.207290	−623.148158	−623.221238
MP4/6–31G**[b]	−300.652039	−300.581113	−300.6666532	−623.254107	−623.199809	−623.267466
MP4/6–311G**	−300.773661	−300.653193	−300.786688	−623.365778	−623.313038	−623.376026
MP4/6–311+G**	−300.788313	−300.716266	−300.800973	−623.378076	−623.323678	−623.386413
MP4/6–311++G**	−300.788712	−300.716651	−300.801402	−623.378510	−623.324174	−623.386937
QCISD/6–311++G**	−300.743591	−300.666334	−300.756407	−623.333233	−623.274771	−623.343394
ZPE	0.082162	0.76434	0.081793	0.075849	0.073369	0.080302
H_{corr}	0.087606	0.081719	0.87376	0.082159	0.078875	0.085933
G_{cor}	0.054512	0.048747	0.053957	0.046348	0.044820	0.051716
S	69.652	69.396	70.335	75.371	71.673	72.015
μ(D)	2.273	3.655	4.534	2.704	4.350	6.513
$E_0 + ZPE$[c]	−300.706550	−300.640217	−300.719609	−623.302661	−623.250805	−623.306635
$E_0 + H_{corr}$	−300.701106	−300.634932	−300.714026	−623.296351	−623.245299	−623.301004
$E_0 + G_{corr}$	−300.734200	−300.667904	−300.747445	−623.332162	−623.279354	−623.335221
ΔH°[d]	−8.107			−2.920		
ΔG°[d]	−8.311			−1.920		
E_a (F)[d]	41.625			32.540		
E_a (R)[d]	49.819			35.034		

[a] Energies, thermal contributions to H° and G° in hartree; S in cal K^{-1} mol^{-1}.
[b] MP4 = MP4SDTQ.
[c] E_0, energy at the MP4SDTQ/6–311 ++ G**//HF/6–31G** level.
[d] ΔH°, ΔG° and E_a in kcal mol^{-1}.

other hand, the bridge in TS(TT) is markedly asymmetric as the corresponding non-bonded distances differ by ca 0.3 Å. In TS(EK) and TS(TT) the internal ring angles are similar to those in the reactant and the product tautomers, whereas the angles involving the exocyclic oxygen and sulfur atoms show large departures from the original species. The animation of the imaginary normal modes, 2359i cm^{-1} for TS(EK) and 2140i cm^{-1} for TS(TT), show that they lead either to the reactants (enol or thiol) or the products (keto or thione). In fact, in both TSs, the hydrogen atom attached to N-3 moves towards or away from the oxygen (or sulfur) atom with a fairly large amplitude of vibration, and synchronously the oxygen or sulfur atoms perform similar movements, although with smaller amplitude of vibration. Accordingly, as the oxygen or sulfur atoms approach the hydrogen atom, the enol tautomeric form is produced, whereas to obtain the products (keto or thione) both hydrogen and oxygen (or sulfur) move away from each other. IRC calculation in the forward or reverse directions led to the enol (or thiol) and keto (or thione), allowing us to conclude that the TSs are fully characterized.

Energetics and thermodynamics

The energetics for the tautomeric reactions of IZ and TIZ calculated at several levels are given in Table 2, from which it can be inferred that the inclusion of electron correlation at the second-order Møller–Plesset theory and using the 6–31G** basis set stabilizes the entire enol–keto system by ca 560 kcal mol^{-1}. A similar stabilization for the thiol–thione system is obtained. On going from MP2 to MP3, additional stabilization of ca 10–15 kcal mol^{-1} takes place for both cases studied here, whereas at the MP4SDTQ level both molecular systems are again stabilized by ca 30 kcal mol^{-1}. Using the triple split valence 6–311G** basis set and including diffuse functions on the heavy atoms, the IZ and TIZ systems gain an additional 70 and 10 kcal mol^{-1}, respectively. When diffusion functions are added to the hydrogens just 0.25 kcal mol^{-1} is gained. Calculations at the QCISD/6–311++G** level did not produce a stabilization comparable to the MP4SDTQ/6–311 ++ G** level. In fact, the QCISD energies are between the MP4SDTQ/6–31G** and MP4SDTQ/6–311G** levels. Enthalpies and free energy changes of ca −8.1 and −8.3 kcal mol^{-1} were calculated for the enol ⇌ keto tautomerization reaction, leading to the conclusion that the keto form is the only species present in the gas phase. For the thiol ⇌ thione reaction, ΔH°_{taut} and ΔG°_{taut} are ca −2.9 and −1.9 kcal mol^{-1}, respectively, implying that although thione is the predominant species in the gas phase, the thiol form is present in ca 4% concentration. For IZ, the calculated activation energies E_a(IZ) for the forward [enol → TS(EK)] and reverse [keto → TS(EK)] reactions are ca 41.6 and 49.2 kcal mol^{-1}, respectively. For TIZ, E_a(F) and E_a(R) are 32.5 and 35.0 kcal mol^{-1}, respectively. Since the activation barrier for thiol → thione interconversion is ca 9 kcal mol^{-1} smaller than that for the enol → keto reaction it seems clear that the former reaction is easier in the gas phase.

Table 3. Solvent effect on the enol ⇌ keto and thiol ⇌ thione systems

Solvent	Enol	Keto	Thiol	Thione
	ΔG_s° (kcal mol^{-1})			
Isooctane (1.90)	−3.99	−3.88	−2.47	−4.33
CCl_4 (2.23)	−4.93	−4.88	−3.17	−5.51
$CHCl_3$ (4.90)	−8.51	−8.57	−5.92	−9.91
THF (7.58)	−9.78	−9.86	−6.93	−11.45
CH_2Cl_2 (8.93)	−10.16	−10.24	−7.23	−11.90
Octanol (10.34)	−10.45	−10.53	−7.47	−12.25
EtOH (24.55)	−11.59	−11.66	−8.39	−13.60
DMSO (46.70)	−12.00	−12.07	−8.73	−14.09
H_2O (78.39)	−12.19	−12.26	−8.88	−14.31
	G°_{soln} (kcal mol^{-1})[a]			
Isooctane	−12.30	−12.19	−4.39	−6.25
CCl_4	−13.24	−13.19	−5.09	−7.43
$CHCl_3$	−16.82	−16.88	−7.84	−11.83
THF	−18.09	−18.17	−8.85	−13.37
CH_2Cl_2	−18.47	−18.55	−9.15	−13.82
Octanol	−18.76	−18.84	−9.39	−14.17
ETOH	−19.90	−19.97	−10.31	−15.52
DMSO	−20.31	−20.38	−10.65	−16.01
H_2O	−20.50	−20.57	−10.80	−16.23
	ΔG°_{soln}	Keto (%)	ΔG°_{soln}	Thione (%)
Isooctane	0.11	45	−1.86	96
CCl_4	0.05	47	−2.34	98
$CHCl_3$	−0.06	52	−3.99	99
THF	−0.08	53	−4.52	100
CH_2Cl_2	−0.08	53	−4.67	100
Octanol	−0.08	53	−4.78	100
EtOH	−0.07	52	−5.21	100
DMS0	−0.07	52	−5.43	100

[a] $G^\circ_{soln} = \Delta G^\circ_{gas} + \Delta G^\circ_s$.

Solvent effect

The solvent effect on the tautomerization reactions reported here was calculated using the PCM method. Solvents of low, medium and high polarities were tried. The solvation free energies (ΔG°_s), free energies in solution (G°_{soln}) and relative values (ΔG°_{soln}) are given in Table 3. The percentages of keto and thione forms present in each solvent are also given. The ΔG°_s values indicate that the keto and enol species are always almost equally solvated, most likely owing to the small differences in dipole moment (ca 2.26 D) and in the total non-electrostatic terms (ca 0.50 kcal mol^{-1}), whereas the thione form would be better solvated than the thiol form. In fact, the thione dipole moment is ca 4 D greater than that of the thiol. The solvent exerts a marked influence on the enol and keto concentrations. The concentration of the enol form increases from ca 1% in the gas phase to ca 48% in the most polar to 55% in the less polar solvent. On the other hand, solvent polarity seems to have very little effect on the thione–thiol system. In fact, for the sulfur-containing system Table 3 shows that the thione tautomer would be easily the most important species both in the gas phase and in solution. Table 4 shows the solvent effect on the activation energies for the forward reactions. The solvent polarity effect on E_a is also strong. In fact, a high-polarity solvent such as water decreases E_a(F) by ca 11–8 kcal mol^{-1} with respect to the value found in the gas phase.

Table 4. Solvent effect on activation energies

	Enol → TS(EK)		Thiol → TS(TT)	
	ΔG°_s[a]	E_a (F)	ΔG°_s[a]	E_a (F)
Gas	—	41.6	—	32.5
Isooctane	−3.50	38.1	−1.90	30.6
CCl_4	−4.39	37.2	−2.55	30.0
$CHCl_3$	−7.80	33.8	−5.03	27.5
THF	−9.03	32.6	−5.93	26.6
CH_2Cl_2	−9.40	32.2	−6.19	26.3
Octanol	−9.68	31.9	−6.31	26.1
ETOH	−10.79	30.8	−7.20	25.3
DMSO	−11.19	30.4	−7.49	25.0
H_2O	−11.38	30.2	−7.62	24.9

[a] TS solvation energy.

CONCLUSIONS

From the above results we can draw the following conclusions.

1. The enol ⇌ keto and thiol ⇌ thione tautomerization reactions are unlikely to occur in the gas phase.
2. The keto and thione tautomers are largely the predominant species in the gas phase.
3. The TSs are planar with H-10 bridging between N-3 and O-6 (or S-6) atoms. In TS(IZ) the bridge is quasi-symmetric, whereas in TS(TIZ) it is asymmetric.
4. The intramolecular proton transfer mechanism takes place more easily in the thiol–thione system, in the gas phase.
5. The enol tautomeric form is present in high concentration (ca 50%) in all solvents studied, whereas the thiol form remains fairly constant at a modest 2–4% concentration.
6. Activation energies are decreased by ca 8–11 kcal mol^{-1} by solvent effects.

The intermolecular proton transfer and solvent-assisted mechanisms are just being explored, although owing to our limited computational facilities the levels of theory most likely will be lower than that used in this work.

Since old UV data indicate that only the keto and thione species are present in high-polarity solvents, experimental information in low- and medium-polarity solvents is called for.

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