THE THIOL/THIONO TAUTOMERISM IN THIOFORMIC ACID: A MOLECULAR ORBITAL STUDY

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The thiol/thiono tautomerism in thioformic acid was investigated using both *ab initio* SCF (6-31G and 6-31++G**) and semiempirical (MNDO, PM3) molecular orbital calculations. In particular, kinetic, thermodynamic and structural properties related to this equilibrium were considered. The structural features were analysed in terms of the molecular charge density topological maps of the thiol, thiono and transition state forms, and correlated with several intramolecular interactions present in these systems. In agreement with experiment, all the methods predicted the thiol tautomer as the most stable form. The kinetic properties and the enthalpy, entropy and free-energy of activation for the tautomeric rearrangement, at 298 K, were evaluated from the potential curves associated with the proton transfer reaction, and the effects of including zero-point energy corrections in the thermodynamic calculations were analysed. The possibility of proton tunnelling was discarded, considering the details of the potential energy profile along the reaction coordinate. Both the semiempirical methods used in this study give a qualitatively correct description of the tautomeric reaction, while they systematically overestimate the relative energy of the thiono tautomer. This overestimation was found to be particularly significant for PM3, but, on the other hand, this method evaluates considerably better the properties of the transition state than the MNDO.**

Keywords: thioformic acid; thiol/thiono tautomerism; SCF-MO calculations.

INTRODUCTION

Nowadays, it is well known the relevance of the tautomeric reactions in a number of different important chemical and biochemical processes[1], such as reactivity of heterocyclic molecules, enzymatic catalysis and spontaneous mutation.

From a theoretical point of view, molecular orbital methods have been of particular importance to further the understanding of tautomeric processes, as they can predict, at a reasonable level of accuracy, the fundamental structural and thermodynamic properties of both the stable tautomers and the transition state[2].

Thioformic acid can exist in two tautomeric forms (the thiol and thiono forms; Fig.1), interconverted by intramolecular proton transfer[3]. Each tautomer has two different stable conformations: the *s-cis* and the *s-trans* forms, corresponding to an X=C-Y-H (X,Y=O or S) dihedral angle of 0° and 180°, respectively. Previous studies on these molecules[3-5] showed that, for both tautomers, the *s-trans* conformers are the high energy forms. Thus, in this work, only the *s-cis* conformers were considered. Moreover, these forms have the correct nuclear arrangement for the intramolecular proton transfer reaction.

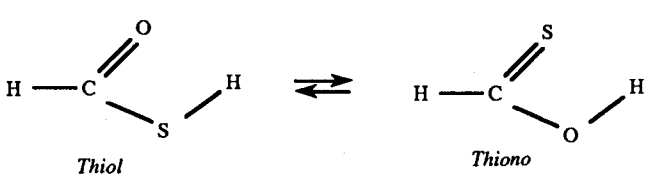


***Figure 1.** Tautomeric forms of thioformic acid.*

The biological importance of both the -C(=O)S- and -C(=S)O- moyeties[6,7] - present in the thiol and thiono tautomers of thioformic acid - led to several recent experimental[8,9] and theoretical[4,5,10] studies on the four stable conformations of this molecule. In fact, thioformic acid is the simplest molecular system which can be used as a model to assess relevant structural and dynamical features of the covalently-bonded-to-enzyme reaction intermediate, named acyl-enzyme[6], formed within the enzyme's active site during some reactions catalysed by cisteine or serine proteases (*eg.*, papain, chymotrypsin)[6,7].

The thiol/thiono tautomerism in thioformic acid was recently studied by *ab initio* calculations[3]. In that study, the geometries of the two tautomers and of the transition state were optimized at the SCF/6-31G** level and their relative energies computed at the MP4/6-31G** level. Particular emphasis was given to the comparison of the results obtained for this molecule with those calculated for the ionized (radical cation) molecule[3].

In the present study the following aspects related with the thiol/thiono tautomerism in thioformic acid are considered:
(i) the structural changes associated with the proton transfer reaction, by analysis of the molecular charge density topological maps of both tautomeric forms and of the transition state;
(ii) the thermodynamic and kinetic properties of the tautomeric reaction, including the evaluation of the potential energy profile associated with the proton transfer;
(iii) the possibility of proton tunnelling.

In a more general perspective, this work also aims to initiate a series of systematic studies whose main purpose consists in the evaluation of the relative performance of the semiempirical (PM3 and MNDO) methods to study tautomeric processes. This systematic approach will enable a judicious

choice of the most reliable method to be used in the study of more complex tautomeric processes, involving larger biochemically important molecules. The fundamental importance of this kind of approach is reinforced by the fact that relevant qualitative differences between the results obtained using different semiempirical methods could be noticed in recent studies on intramolecular tautomerization reactions of 2-pyrrol thiocarboxyaldehyde and 2–pyridone = 2–hydroxypyridine[11].

COMPUTATIONAL METHODS

The Hartree–Fock SCF–MO calculations were performed in a VAX 8700 computer using the GAUSSIAN 86 program system[12] and the 6–31G** and 6-31++G** basis sets[13]. These bases provide a good compromise between computer time and the quality of the results[4]. The molecular geometries for the various molecules were evaluated using the standard methods of GAUSSIAN 86, until the maximum residual internal coordinate forces were less than $3x10^{-4}$ hartree $bohr^{-1}$ (1 hartree= 2625.5001 kJ mol^{-1}; 1 bohr= $5.29177x10^{-11}$ m) or hartree rad^{-1}. The stopping criterion for the SCF iterative process required a density matrix convergence of less than 10^{-8}. The calculations carried out using the 6-31++G** basis enabled us to measure the effect of including diffuse functions in the basis set on the properties of the transition state structure. In this structure, the proton is more loosely bound and, thus, it could be expected that diffuse functions might be particularly important. However, the results obtained with or without considering diffuse functions do not differ significantly, as it will be stressed later on.

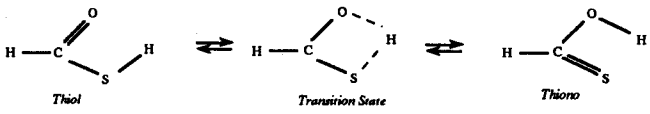
The semiempirical calculations (MNDO[14] and PM3[15]) were performed using the VAX version of the MOPAC/5 program[16].

The analysis of the wave functions in terms of the charge distribution was carried out by the Bader's topological method[17,18] using the PROAIM package[19], adapted to the VAX/VMS system.

RESULTS AND DISCUSSION

Structural features

The equilibrium geometries of the relevant forms to the tautomeric reaction were calculated both at the *ab initio* SCF



(6–31G** and 6-31++G**) and semiempirical (MNDO and PM3) levels of theory. The results are presented in Table 1.

Generally speaking, the semiempirical methods predict the geometries of all the studied molecules in good agreement

Table 1. Equilibrium geometries for the forms relevant to the tautomeric reaction.

Coordinate	SCF (6-31G**)	SCF (6-31++G**)	Δ	MNDO	Δ	PM3	Δ
HC(=O)SH							
C-H	109.1	109.1	0.0	110.7	1.6	110.4	1.3
C-S	177.5	177.1	-0.4	169.6	-7.9	178.3	0.8
C-O	118.0	118.2	0.2	122.0	4.0	120.4	2.4
S-H	132.6	132.7	0.1	130.3	-2.3	130.6	-2.0
H-C-O	123.5	123.0	-0.5	123.1	-0.4	121.3	2.2
H-C-S	111.4	111.6	0.2	110.6	-0.8	109.1	-2.3
S-C-O	125.1	125.4	0.3	126.3	1.2	129.6	4.5
C-S-H	96.0	96.2	0.2	105.5	9.5	104.1	8.1
Transition State							
C-H	108.0	108.0	0.0	109.0	1.0	109.1	1.1
C-S	169.5	169.3	-0.2	164.4	-5.1	167.8	-1.7
C-O	123.5	123.6	0.1	127.7	4.2	128.2	4.7
O-H	132.4	132.2	-0.2	130.8	-1.6	136.3	3.9
S-H	164.1	164.2	0.1	164.8	0.7	176.2	12.1
H-C-O	121.9	121.9	0.0	124.4	2.5	118.6	-3.3
H-C-S	127.7	127.8	0.1	130.3	2.6	132.5	4.8
S-C-O	110.4	110.3	-0.1	105.3	-5.1	108.9	-1.5
C-O-H	80.9	81.0	0.1	86.2	5.3	86.7	5.8
C-S-H	59.7	59.7	0.0	64.9	5.2	63.7	4.0
HC(=S)OH							
C-H	107.8	107.7	-0.1	110.4	2.6	110.3	2.5
C-S	161.9	161.8	-0.1	156.4	-5.5	159.1	-2.8
C-O	130.6	130.7	0.1	134.1	3.5	133.8	3.2
O-H	95.0	95.0	0.0	95.1	0.1	95.5	0.5
H-C-O	110.5	110.5	0.0	110.5	0.0	104.1	-6.4
H-C-S	122.9	122.9	0.0	122.8	-0.1	125.8	2.9
S-C-O	126.6	126.6	0.0	126.7	0.1	130.1	3.5
C-O-H	110.2	110.6	0.4	114.6	4.4	110.6	0.4

Distances in pm; angles in degrees. Δ= differences with respect to 6-31G** SCF *ab initio* values.

with those obtained at the *ab initio* SCF level. The largest differences occur in the calculated values of the C–O distance and of the H–O–C angle. For instance, the C–O distance obtained using both the MNDO and PM3 semiempirical methods for the transition state structure is *ca.* 128 pm, while the 6–31G** *ab initio* SCF value is 123.5 pm. On the other hand, it is interesting to point out that the PM3 and *ab initio* SCF C–S distances are in quite good agreement, while the MNDO method considerably underestimates these distances (see Table 1). In addition, the inclusion of diffuse functions in the basis set does not lead to significant differences in the geometrical parameters, even for the transition state structure.

From a structural point of view, all methods indicate that the transition state resembles more the thiol than the thiono tautomer, with the transferred proton closer to that observed for the thiol than for the thiono form. For example, while the lengthening of the S–H bond going from the thiol tautomer to the transition state amounts to 31.5 pm (SCF 6-31G**), the equivalent change in the O–H bond length going from the thiono to the transition state is 37.4 pm, thus being slightly larger than that observed for the S–H bond. Obviously, the percentual changes in these bond lengths (*ca.* 39% and 24%, respectively for O–H and S–H distances) reflect more clearly the greatest similarity between the structures of the thiol tautomer and the transition state.

The effects of the proton transfer reaction on the structural properties of the thioformic acid molecule can also be evaluated by looking at the molecular charge density topological maps (*ab initio* SCF; 6–31G**) shown in Fig. 2. In these maps, the isodensity lines A and B are those which better reflect the breaking down and the formation of the chemical bonds accompayning the tautomeric reaction:

(i) When the reaction proceeds from the thiono to the thiol tautomer, the density line B exhibits a narrowing in the contour in between the C and the S atoms, thus reflecting the break down of the C=S double bond.

(ii) The density line A between the C and O atoms, which in the thiono form is separated in two components, shows a single component between these atoms in the thiol form. This reflects the formation of the C=O double bond.

It has been shown that *ab initio* SCF-MO calculations are able to reproduce very well the experimentally observed differences in the length of CH bonds having different chemical environments[20,21]. Thus, another interesting structural feature associated with the studied tautomeric process is the systematic increase of the CH bond length in going from the thiono to the thiol tautomer (see Table 1 and Fig.2). This lengthening of the CH bond is well predicted by all methods, though the semiempirical ones seem to overestimate the CH bond length in the thiono form (in particular, these methods yield the CH bond length longer in the thiono form than in the transition state, contrarily to the results obtained at the *ab initio* SCF level). The longer CH bond length of the thiol form is a consequence of the anomeric effect involving an electron charge transfer from the carbonyl lone–pair in *trans* position to the σ^*(CH) antibonding orbital[20]. It is easy to understand that, because a C=S bond is much longer than a C=O bond, a similar interaction, in the thiono tautomer, involving the sulphur lone–pair should be considerably less important than the above mentioned interaction. The oxygen lone–pair/σ^*(CH) interaction leads also to (i) an increase of the charge density on the formyl hydrogen atom, (ii) a large intensification of the infrared absorption band associated with the CH stretching vibration, and (iii) a decrease of the vibrational frequency of this mode (see Table 2). These results agree with previous data on similar molecules[21-25], and reflect the weakening of the CH bond in going from the thiono to the thiol tautomer. Using the McKean relationships[20], this weakening is estimated to correspond to *ca.* 42 kJ mol^{-1}.

Table 2. Atomic charges on the formyl hydrogen atom, frequencies and infrared intensities of the C-H stretching vibration as calculated at the 6-31G** SCF level.

Tautomer	q(H)	ν(C-H)	A(C-H)
Thiol	0.088	3188	66.8
Thiono	0.145	3348	11.8

Charges in electrons ($e \approx 1.60 \times 10^{-19}$ C); frequencies in cm^{-1}; infrared intensities in km mol^{-1}.

Thermodynamic and kinetic properties

Table 3 shows the calculated values for the enthalpy, entropy and free–energy changes associated with the tautomeric reaction, at 298 K, corrected by zero–point energy contributions. Generally speaking, the results obtained by the various methods used in this study show a qualitative agreement, though the semiempirical methods overestimate the relative difference in energy between the thiono and the more stable thiol form (PM3 in particular). The *ab initio* SCF calculations predict a relative population of the thiono tautomer of 6.4%, which is in good agreement with the experimental value previously obtained using infrared and NMR spectroscopic methods (4%[26]).

Table 3. Calculated entalphy, entropy and free energy changes (in kJ mol^{-1}, J K^{-1}mol^{-1}, and kJ mol^{-1}) for the thiol-thiono tautomeric arrangement in thioformic acid, at 298 K, including zero-point energy corrections.

	ΔH	ΔS	ΔG
MNDO	29.7	-1.284	30.0
PM3	100.9	-4.494	102.2
SCF (6-31G**)	16.2	-4.238	17.5
SCF (6-31++G**)	18.5	-4.084	19.9

Figures 3 and 4 show the potential energy profiles associated with the proton transfer reaction calculated with the MNDO and PM3 methods, respectively. The equilibrium geometries of the two tautomers and that of the transition state structure define three critical points along the intrinsic reaction coordinate. The analysis of the structural changes in the geometries of the two tautomers due to the proton transfer reaction near the corresponding energy minima allows a clear identification of their dissociative normal coordinates (see Figs. 3 and 4). The characterization of these coordinates were confirmed by comparing the values of their force constants with those resulting from a second order polynomial adjustment of the potential energy profile near the associated energy minimum. An interesting feature shown by the calculated intrinsic reaction coordinates (mainly that obtained using PM3) is their high degree of harmonicity. In fact, from Figs. 3 and 4 it is clear that the calculated reaction potential energy profiles can be practically fitted by two parabolas associated with the minima.

Both the PM3 and MNDO methods calculated the first vibrational energy levels, for both tautomers, as being separated by *ca.* 5-6 kJ mol^{-1} (*ca.* 420-500 cm^{-1}) a quite small value when compared with the reaction energy barriers (> 45 kJ mol^{-1}; see also Figs. 3,4). On the other hand, the distance between the energy minima along the reaction coordinate is considerably large (*ca.* 250 pm). Thus, the possibility that the reaction proceeds via proton tunnelling can be discarded.

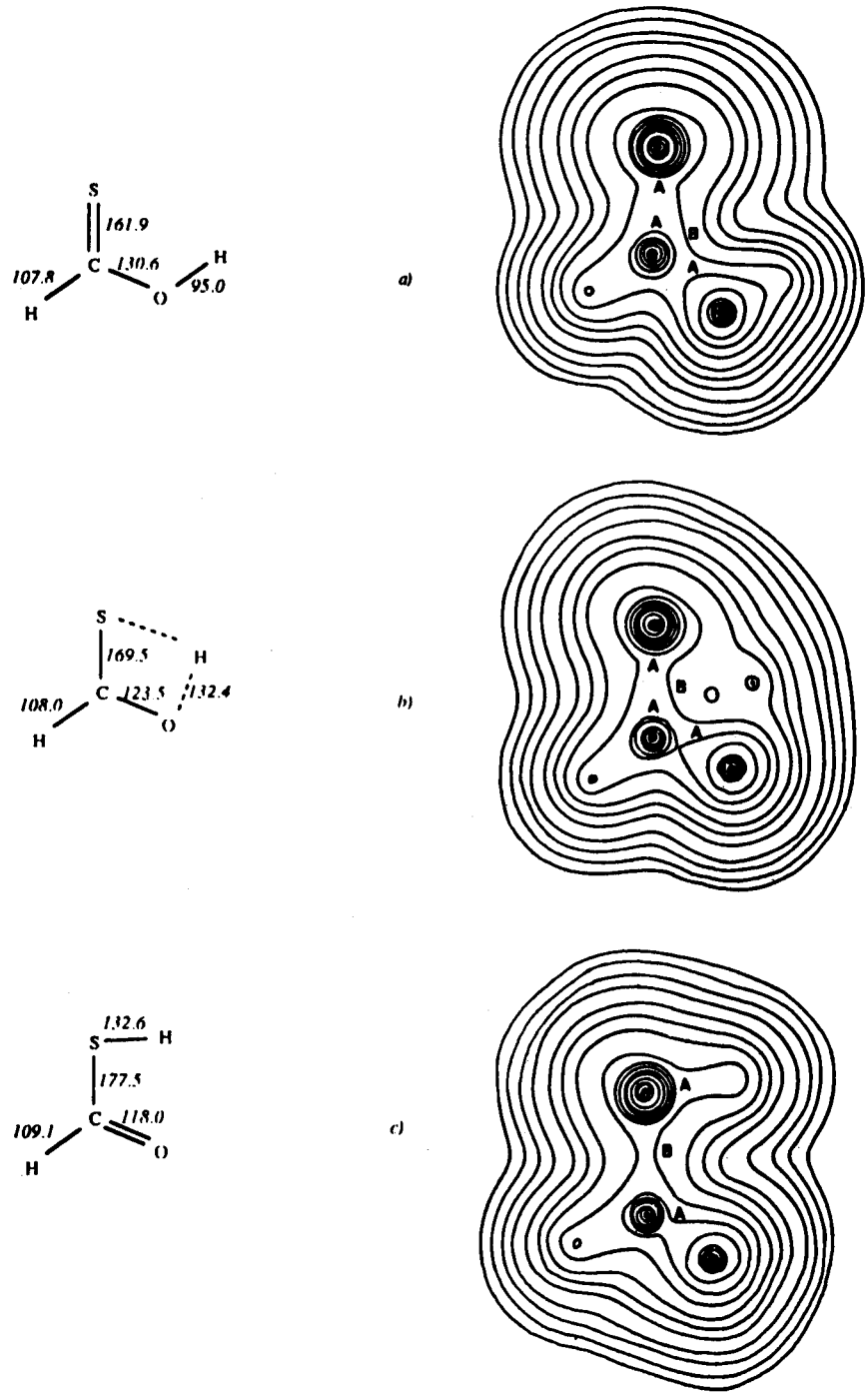


Figure 2. *Contour plots of the electronic charge distributions in the molecular plane calculated from the 6-31G** wavefunctions for a) thiono, b) transition state and c) thiol structures.*

Table 4 shows the calculated transition thermodynamic properties, corrected for zero-point energy contributions. With the exception of $\Delta H^{\ddagger}$(transition state–thiono), the PM3 calculated values agree quite well with the *ab initio* SCF 6–31G** results. $\Delta H^{\ddagger}$(transition state–thiono) is underestimated (*ca.* 38%) by this method mainly due to the fact that it substantially overestimates the energy of the thiono form, as it was already previously mentioned. On the other hand, the MNDO method systematically overestimates the transition state properties with respect to both tautomers by more than 33%. Thus, the energy barriers for the isomerization reactions calculated using this method are considerably higher than those obtained using the other methods, leading also to smaller rate constants for these processes (Table 5). Interestingly, the MNDO calculated equilibrium constant is closer to the *ab initio* SCF value than that obtained with the PM3 method (see Table 5), as the errors in the rate constants (k_1 and k_{-1}) partially compensate each other (obviously, this result can also be correlated with the better performance of the MNDO method in calculating the relative energy of the two tautomers when compared with PM3, as it was pointed out above).

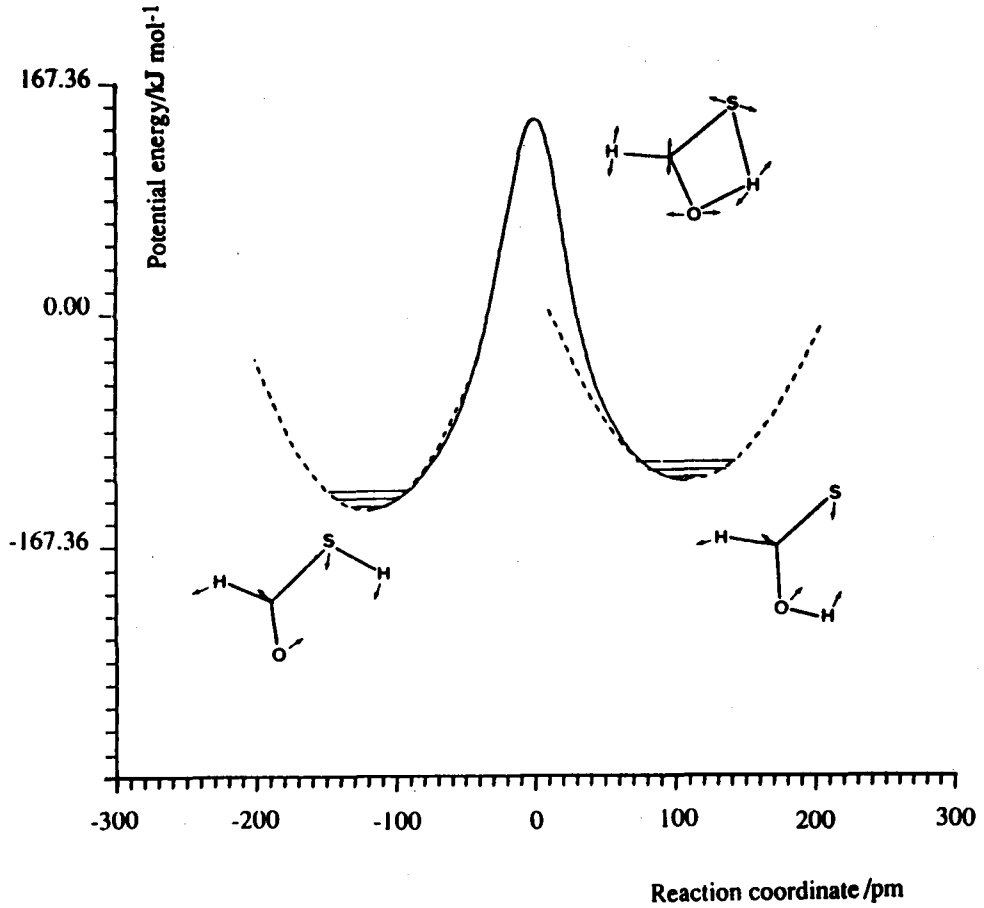


Figure 3. Potential energy profile associated with the proton transfer reaction calculated with the MNDO method, showing the dissociative normal coordinates of the relevant structures. The force constants and energy differences between consecutive vibrational energy levels associated with the parabolas shown in the figure are respectively 0.216x10³ N cm⁻¹ and 5.10 kJ mol⁻¹ (426 cm⁻¹), for the thiol form, and 0.269x10³ N cm⁻¹ and 5.10 kJ mol⁻¹ (426 cm⁻¹), for the thiono form.

Table 4. Calculated transition entalphy, entropy and free energy changes (in kJ mol^{-1}, J K^{-1}mol^{-1}, and kJ mol^{-1}) for the thiol-thiono tautomeric rearrangement in thioformic acid, at 298 K, including zero-point energy corrections.[a]

		ΔH‡	ΔS‡	ΔG‡
Thiol→Thiono	MNDO	260.4 (38)	-8.933 (38)	263.0 (37)
	PM3	207.9 (10)	-7.251 (12)	210.1 (10)
	SCF $_{(6\text{-}31++G^{**})}$	190.1 (<1)	-6.447 (<1)	192.0 (<1)
	SCF $_{(6\text{-}31G^{**})}$	189.4	-6.473	191.4
Thiono→Thiol	MNDO	230.7 (33)	-7.648 (242)	233.0 (34)
	PM3	107.1 (38)	-2.757 (23)	107.9 (38)
	SCF $_{(6\text{-}31++G^{**})}$	171.6 (<1)	-2.363 (<1)	172.3 (<1)
	SCF $_{(6\text{-}31G^{**})}$	173.2	-2.234	173.9

[a] Values in parenthesis are the % errors with respect to the 6–31G** SCF values.

The importance of including zero–point contributions to calculate transition state thermodynamic properties and the relative lack of importance of entropy in tautomeric rearrangements

In general, when dealing with relative stabilities of different tautomeric forms, both zero–point energy corrections and entropy changes are not considered. This approximation is usually taken under the assumption that the reaction entropy changes and the zero–point energy corrections are negligible, or that they mutually cancel out. It has been proposed that the error of neglecting the zero–point energy contributions in calculating energetic properties associated only with minimum energy conformations are usually less than 21 kJ mol^{-1} [1]. However, to the best of our knowledge, no similar estimate has yet been derived for energy differences involving transition state structures or for kinetic data in general.

The zero–point energy corrections to thermodynamic and kinetic properties obtained in the present study are shown in Table 6. The zero–point corrections to the thermodynamic

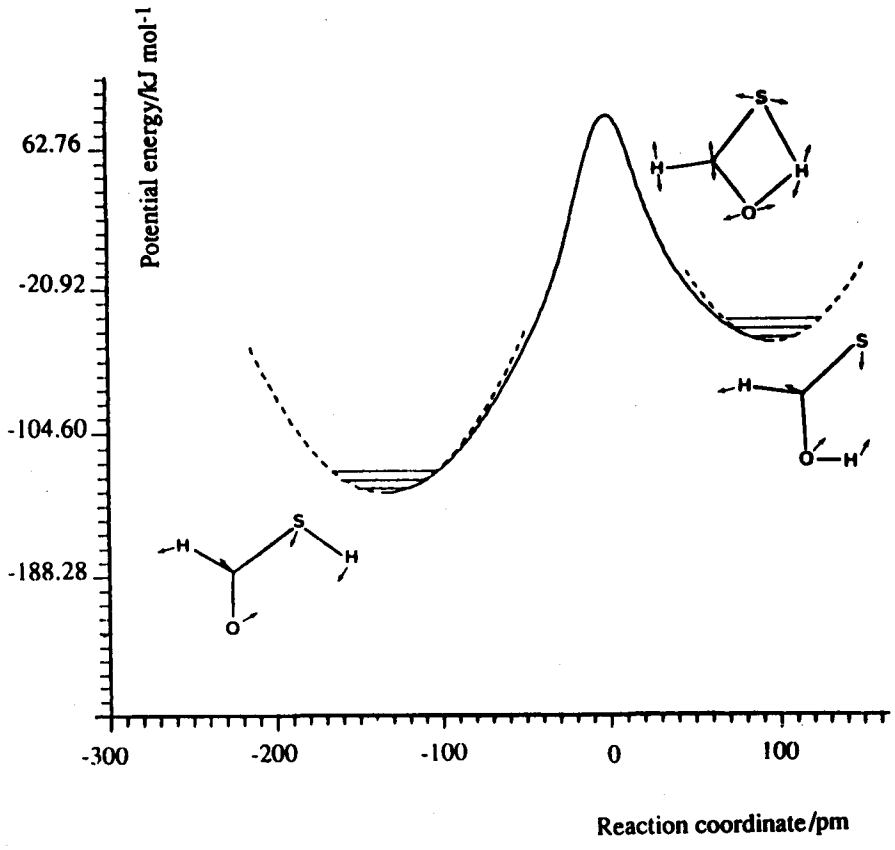


Figure 4. Potential energy profile associated with the proton transfer reaction calculated with the PM3 method, showing the dissociative normal coordinates of the relevant structures. The force constants and energy differences between consecutive vibrational energy levels associated with the parabolas shown in the figure are respectively 0.283x10³ N cm⁻¹ and 5.69 kJ mol⁻¹ (476 cm⁻¹), for the thiol form, and 0.207x10³ N cm⁻¹ and 5.52 kJ mol⁻¹ (461 cm⁻¹), for the thiono form.

Table 5. Calculated equilibrium (K) and rate constants (k_1 and k_{-1}) for the tautomeric rearrangement in thioformic acid.[a]

	K	thiol→thiono k_1/s^{-1}	thiono→thiol k_{-1}/s^{-1}
MNDO	$5.45x10^{-6}$	$4.82x10^{-34}$	$8.85x10^{-29}$
PM3	$1.20x10^{-18}$	$4.48x10^{-27}$	$3.73x10^{-9}$
SCF $_{(6\text{-}31G^{**})}$	$8.59x10^{-4}$	$1.73x10^{-21}$	$2.01x10^{-18}$
SCF $_{(6\text{-}31++G^{**})}$	$3.54x10^{-4}$	$1.36x10^{-21}$	$3.84x10^{-18}$

[a] Rate constants were calculated using the formula $(kT/h)\exp(-\Delta G^{\ddagger}/RT)$.

properties of the equilibrium forms lie under the limit proposed in ref. 1, the largest value corresponding to that obtained using the PM3 method (15.5 kJ mol^{-1}). However, the zero–point corrections to the transition properties are considerably larger at all levels of calculation, going to more than 31.7 kJ mol^{-1} in the case of the $\Delta H^{\ddagger}$ for the thiono→thiol conversion obtained using the MNDO method (see Table 6). In fact, the zero–point energy correction terms are mainly due to different values of the force constants in the critical point structures. Obviously, this becomes particularly important when the properties of the transition state are considered, as the dissociative normal mode – which corresponds to a negative force constant – can not contribute to the vibrational zero–point energy.

Table 6. Entropy changes and zero-point energy corrections (kJ mol^{-1}) to the thermodynamic and kinetic properties associated with the thiol-thiono tautomeric rearrangement in thioformic acid, at 298 K.

		MNDO	PM3	SCF 6-31++G**	SCF 6-31G**
Thiono–Thiol	$\Delta H^{vib(0)}$	8.95	15.52	10.50	10.71
	$-T\Delta S$	0.38	1.34	1.23	1.26
Thiol→Thiono	$\Delta H^{\ddagger vib(0)}$	-22.76	-13.18	-6.91	-6.90
	$-T\Delta S^{\ddagger}$	2.68	2.18	1.92	1.92
Thiono→Thiol	$\Delta H^{\ddagger vib(0)}$	-31.71	-28.70	-17.41	-17.61
	$-T\Delta S^{\ddagger}$	2.26	0.84	0.70	0.67

From the results shown in Table 6 it can also be concluded that the entropy changes (both $T\Delta S$ and $T\Delta S^{\ddagger}$) in a tautomeric reaction are close to zero for the usual range of temperatures. This is consistent with the geometrical nature of the molecular rearrangements associated with these processes.

CONCLUSION

The results indicate that the transition state of the tautomeric reaction in thioformic acid resembles more the thiol than the thiono form, with the transferred proton closer to that observed for the thiol than for the thiono tautomer.

The *ab initio* SCF 6–31G** calculations predict 6.4% of the thiono form in the equilibrium, at 298 K, in good agreement with the experimental value (4%[24]) and with a previously obtained theoretical value which included electron correlation (MP4/6–31G**; 5.1%[3]). On the other hand, while both the semiempirical methods used in this study (MNDO and PM3) give a qualitatively correct description of the tautomeric reaction, they systematically overestimate the relative energy of the thiono tautomer. This overestimation is, however, particularly significant for the PM3 result (ΔH is six times larger than the SCF value, whereas the MNDO one is only about twice larger), though this method evaluates better the properties of the transition state than the MNDO. In addition, the inclusion of zero–point energy corrections was shown to be important to the properties of the transition state at all levels of calculation. In particular, this correction appears to be more relevant than those related with the stable tautomers.

From the analysis of the potential energy profile associated with the intramolecular proton transfer reaction, and considering the relative energies of the reaction barrier, those of the first energy levels in both tautomers, and the distance between the two energy minima along the reaction coordinate, the possibility that the studied reaction proceeds *via* proton tunnelling was discarded.

Finally, a new method, based in chemometric techniques, is now being developed in our laboratories, to minimize systematic errors in the calculation of kinetic and thermodynamic properties by semiempirical methods. Chemometric methods, like the Partial Least Squares (PLS) method[26], have been used successfully also to fit theoretical data, like equilibrium molecular geometries and infrared intensities, to the corresponding experimental values[27,28]. Though the amount of data currently available is not yet enough to reach definitive conclusions, the present results give further support to our previous suggestion[11] that the errors in the semiempirical calculated thermodynamic and kinetic properties associated with tautomeric reactions are essentially systematic. Thus, we are now considering the application of a coupled semiempirical/PLS methodology to the study of this kind of processes.

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