Gas-Phase Basicity of 2,7-Dimethyl-[1,2,4]-Triazepine Thio Derivatives

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Received: March 21, 2002; In Final Form: May 29, 2002

The gas-phase proton affinities of 3-thio-5-oxo, 5-thio-3-oxo, and 3,5-dithio derivatives of 2,7-dimethyl-[1,2,4]-triazepine have been measured by means of Fourier transform ion cyclotron resonance (FTICR) mass spectrometry. The structures and vibrational frequencies of all the stable protonated tautomers and all the transition states connecting them have been obtained by means of the B3LYP density functional method, together with a 6-31G* basis set expansion. The final energies were obtained at the B3LYP/6-311+G(3df,-2p) level. In contrast with the results from the analogous thiouracils, our results indicate that all of these compounds behave as sulfur bases in the gas phase. For 5-thio-3-oxo-[1,2,4]-triazepine and 3,5-dithio-[1,2,4]-triazepine, the thiol−enol and the dithiol forms are the most stable protonated species, respectively. Conversely, for 3-thio-5-oxo-[1,2,4]-triazepine, the thiol−ketone form is the most stable one. For 5-thio-3-oxo-[1,2,4]-triazepine and 3,5-dithio-[1,2,4]-triazepine, as it was found for thiouracils, a comparison between theoretical and experimental proton affinities suggests the formation of dimers between protonated and neutral species, which favors proton-transfer mechanisms leading to the formation of the most stable protonated species.

Introduction

In the last three decades, a great deal of attention was devoted to the measurement of gas-phase basicities.[1−9] Many of these studies dealt with bases that have several basic centers, such as oxygen, nitrogen, and sulfur atoms, so the first problem addressed was the unambiguous characterization of the basic centers and the possible role of the nature of the Lewis acid on their intrinsic reactivities. An interesting example is provided by thiouracil derivatives because, on one hand, protonation on the oxygen atoms may compete, in some cases, with protonation on sulfur; on the other hand, the most stable protonated form cannot be obtained by direct protonation of the neutral species.[10] This means that a rationalization of their gas-phase basicity required a thorough analysis of the equilibria between the different tautomers of both the neutral and the protonated species. These facts prompted us to investigate the gas-phase basicity of the thio derivatives of 2,7-dimethyl-[1,2,4]-triazepine that have a remarkable resemblance to thiouracils. Very little is known about the structures, relative stability, or intrinsic reactivity of triazepines, although various oxo and thio derivatives have been used as starting materials in the synthesis of fused heterocyclic systems of potential pharmacological activity.[11,12] In fact, only a few mass spectrometry studies on the unimolecular fragmentation of [1,2,4]-triazepines,[13,14] the X-ray diffraction determination of the structure of some [1,2,4]-triazepine and 1,3,4-triazepine derivatives,[15−17] and the complexes formed from [1,2,4]-triazepines with ruthenium (II)[18] have been reported in the literature. Quite surprisingly, the basicity of [1,2,4]-triazepines is not well documented, probably because of difficulties associated with the synthesis of these compounds. This fact and our longstanding interest in sulfur-containing bases[10,19,20] have prompted us to investigate their intrinsic (gas-phase) basicities.

As uracil and thiouracil derivatives,[10,21−25] the [1,2,4]-triazepines under investigation may exhibit five different tautomeric forms (see Scheme 1) with different conformations.

In a recent study,[26] we have shown that the most stable conformer corresponds to the oxo-thione or the dithione. We have also found[26] that the barriers between the different tautomers are high enough to assume safely that only the oxo-thione or the dithione structures will be present in the gas phase. The number of conformers increases upon protonation, where the 12 different arrangements shown in Figure 1 can be envisaged. Hence, the first goal of our study will be a complete analysis of the relative stability of these tautomers and of the barriers connecting them. This will allow us to identify the most stable protonated forms and therefore to estimate the proton affinity of each of the compounds under scrutiny. These estimates will be then compared with the experimental values obtained by means of ion cyclotron resonance spectrometry (FTICR) techniques.[5,27−29]

Experimental Section

Chemicals. The synthesis of the various triazepines under investiagtion was performed by using the procedures reported in the literature. The preparation of 2,7-dimethyl-3-thioxo-5-oxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine (**3S5O**) has been reported for the first time by Loss et al.[30] and refined by

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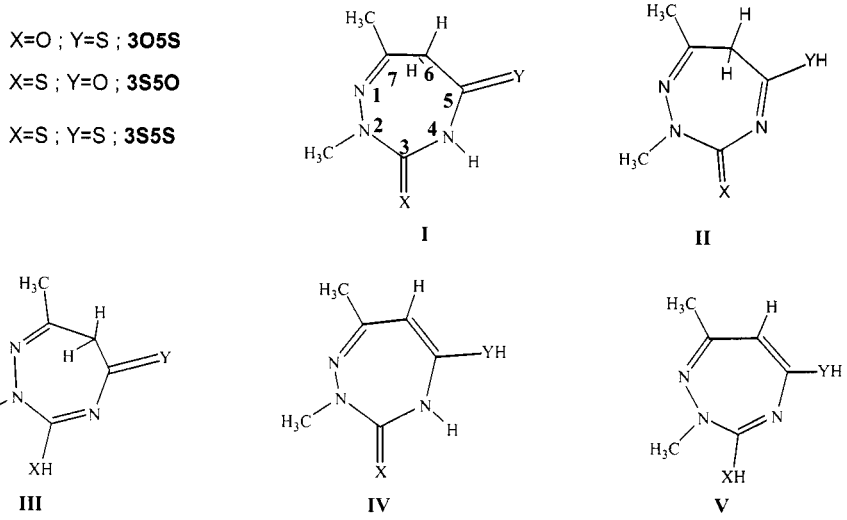
10.1021/jp0207782 CCC: $22.00
Published on Web 07/23/2002

SCHEME 1



Hasnaoui et al.[13,15,31,32] They treated 2-methylthiosemicarbazide with ethylacetylacetate to produce the corresponding thiosemicarbazone. The latter intermediate then gave **3S5O** by a cyclization reaction using sodium in propan-2-ol. Then, the resulting triazepine **3S5O** was treated with phosphorus pentasulfide in refluxing acetonitrile to yield 2,7-dimethyl-3,5-dithioxo-3,4,5,6-tetrahydro-2H-1,2,4- triazepine (**3S5S**). The condensation of **3S5O** with mesitylnitrile oxide in dry diethyl ether yielded the corresponding [1,2,4]-triazepin-3,5-dione. Treatment of the latter with phosphorus pentasulfide in refluxing dry pyridine afforded 2,7 dimethyl-3-oxo-5-thioxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine (**3O5S**).[31,33] Compounds **3S5S** and **3O5S** were purified first with column chromatography on silica gel (eluent, diethyl ether/petroleum ether) and second by recrystallization from ethanol.

2,7-Dimethyl-3-thioxo-5-oxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine (3S5O): yield: 83%, F = 136−137 °C (propan-2-ol), ^{1}H NMR ($CDCl_3$, δ): 2.30 (s, 3H, C7−CH_3); 3.80 (s, 3H, N2−CH_3); 3.50 (s, 2H, C6−H); ^{13}C NMR ($CDCl_3$, δ): 23.2 (C7−CH_3), 42.9 (C6), 45.5 (N2−CH_3), 162.3 (C5), 163.5 (C7), 173.8 (C3); MS (M^+) m/e = 171. Anal. $C_6H_9N_3SO$: C, 42.50; H, 5.30; N, 24.10.

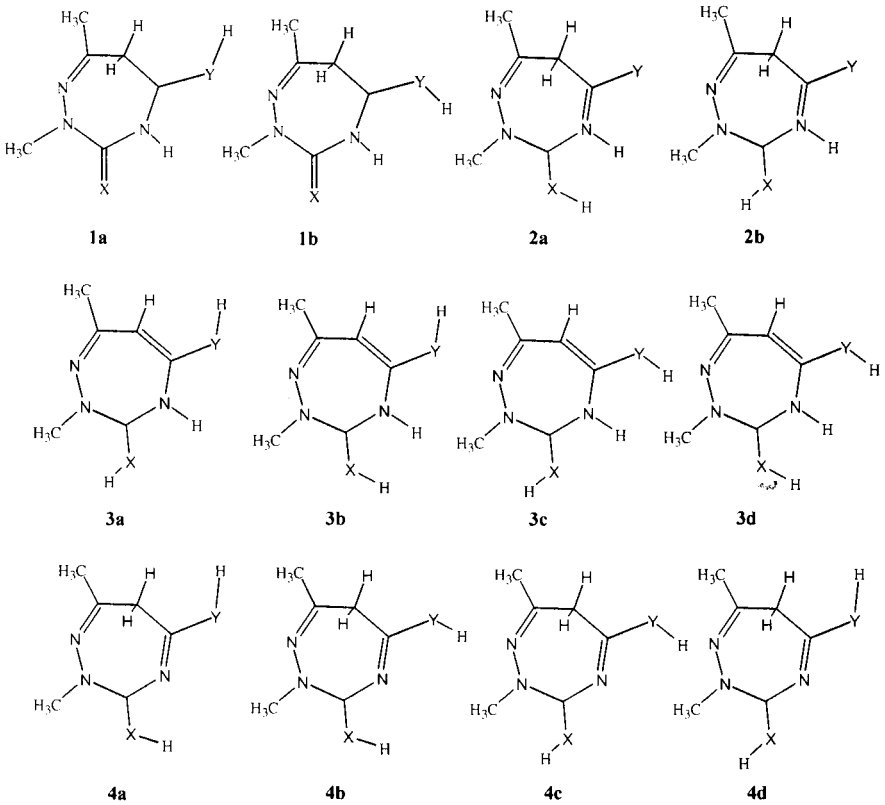


Figure 1. Twelve tautomers of the protonated forms of thiotriazepines.

TABLE 1: Experimental Determination of the Gas-Phase Basicities of Selected Triazepines[a]

compound	standard reference	GB (std)[b]	$\delta\Delta G_{H+}$ (g)	GB	GB (average)
3S5O	isophorone	206.12	−0.84	206.96	
	$(t\text{-}C_4H_9)_2S$	206.70	−0.10	206.80	206.8 ± 2
	$c\text{-}C_3H_5NH_2$	208.11	1.49	206.62	
3S5S	$c\text{-}C_3H_5NH_2$	208.11	−0.23	208.34	208.1 ± 2
	2-chloropyridine	207.89	0.01	207.88	
3O5S	2-fluoropridine	203.99	0.60	203.39	203.5 ± 2
	4-cyanopyridine	203.06	−0.46	203.52	

[a] All values in kcal mol^{-1}. [b] Data from ref 7.

2,7-Dimethyl-3,5-dithioxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine (3S5S): yield: 70%, F = 141−142 °C (propan-2-ol), ^{1}H NMR ($CDCl_3$, δ): 2.27 (s, 3H, C7−CH_3); 3.70 (s, 3H, N2−CH_3); 3.88 (s, 2H, C6−H); ^{13}C NMR ($CDCl_3$, δ):22.6 (C7−CH_3), 45.6 (N2−CH_3), 51.4 (C6), 164.6 (C7), 172.7 (C3), 194.6 (C5); MS (M^+) m/e = 187. Anal. $C_6H_9N_3S_2$: C, 38.42; H, 4.84; N, 22.33.

2,7-Dimethyl-3-oxo-5-thioxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine (3O5S): yield: 40%, F = 147−148 °C (EtOH), ^{1}H NMR ($CDCl_3$, δ): 2.33 (s, 3H, C7−CH_3); 3.76 (s, 3H, N2−CH_3); 3.86 (s, 2H, C6−H); MS (M^+) m/e = 171. Anal. $C_6H_9N_3SO$: C, 42.08; H, 5.43; N, 24.49.

Gas-Phase Basicities. The gas-phase basicities, GB, were determined from equilibrium proton-transfer reactions conducted in a modified Bruker CMS-47 Fourier transform ion cyclotron resonance (FTICR) mass spectrometer[2] under conditions similar to those described in the literature.[19,34] Table 1 presents the results of proton-transfer equilibria (1) obtained in this study along with the standard bases used (B_{ref}).

$$B_{ref}H^+(g) + B(g) \rightleftharpoons BH^+(g) + B_{ref}(g) \qquad K_p,\ \delta\Delta G^\circ_{H+}(g) \tag{1}$$

In reaction 1, B refers to a neutral triazepine. At least two reference bases were used in each case. The GB values for the reference bases were taken from the most recent critical compilation.[7] The gas-phase proton basicity, GB, of B is the negative of $\Delta G^\circ_{H+}(g)$, the standard Gibbs energy change for reaction 2:

$$B(g) + H^+(g) \rightarrow BH^+(g) \qquad \Delta G^\circ_{H+}(g),\ \Delta H^\circ_{H+}(g) \tag{2}$$

The proton affinity (PA) of the same base is the negative of $\Delta H^\circ_{H+}(g)$. GB values are obtained by combining $\delta\Delta G^\circ_{H+}(g)$ data with the GB of the reference bases.

Ion selection experiments were performed in all cases. They showed the reversibility of reaction 1.

The pressure readings for the neutral reactants as determined by the Bayard−Alpert gauge were corrected with the gauge sensitivity factor[35] using the average molecular polarizability α (ahc) calculated according to Miller.[36]

Consideration of the experimental data indicates that GB values are determined with respect to the anchoring references with a precision of 0.2−0.3 kcal mol^{-1} or better. The "absolute" GB values have estimated accuracies of ca. 2 kcal mol^{-1}. [7]

To obtain the proton affinities (PAs) from the measured GBs, we have used the entropy values and the thermal corrections obtained in our DFT calculations, at the B3LYP/6-31G* level, for the corresponding neutral and protonated species. For H^+, a value of S = 26.039 cal mol^{-1} K^{-1} was employed. A temperature of 298.2 K was assumed.

Computational Details

Standard DFT calculations, in the framework of the B3LYP approach, have been carried out by using the Gaussian 98 suite of programs.[37] The B3LYP method combines Becke's three-parameter nonlocal hybrid exchange potential[38,39] with the nonlocal correlation functional of Lee, Yang, and Parr.[40] This approach has been shown to provide geometries in fairly good agreement with experimental values,[41−44] whereas the harmonic vibrational frequencies are closer to experiment than those obtained by using other correlated methods such as MP2.[45,46] Proton affinities estimated by using a quite flexible basis set expansion, such as the 6-311+G(3df,2p) are in good agreement[47−49] with the experimental values, although in general the B3LYP values usually overestimate[48,50,51] the experimental ones by about 2 kcal mol^{-1}, on average.

The B3LYP/6-31G* optimized geometries of the most stable tautomers of **3S5O**, **3O5S**, and **3S5S** were reported in a previous paper.[26] Hence, we shall concentrate our attention on the corresponding protonated species. For this purpose, we considered all possible tautomers (structures **1**−**4** in Figure 1) in all possible conformations, which have been identified by adding a, b, c, or d to the number that designates the corresponding conformer. As shown in Figure 1, a total of twelve different structures were fully optimized at the B3LYP/6-31G* level for each compound. The corresponding harmonic vibrational frequencies were evaluated at the same level of theory to assess whether all structures found corresponded to local minima of the PES and to estimate the corresponding zero-point energy (ZPE) corrections that were scaled by the empirical factor 0.9806 that was proposed by Scott and Radom.[52] A similar procedure was adopted to locate the transition states associated with the different tautomers.

To obtain more reliable energies, we have performed single-point energy calculations at the B3LYP/6-311+G(3df,2p) level of theory. The corresponding values for the neutrals were taken from ref 26.

Net atomic charges of the most stable tautomers were analyzed by means of the natural bond orbital (NBO)[53] technique.

Results and Discussion

The B3LYP/6-311+G(3df,2p)//B3LYP/6-31G* total energies and the ZPE corrections obtained at B3LYP/6-31G* are given in Table 2 for each of the species investigated. Optimized geometries of the 36 structures investigated are available from the authors upon request.

To study the gas-phase basicity of the triazepine thio derivatives, it is convenient to recall that for **3S5O** and **3O5S** the tautomers' stability order is **I** > **IV** > **II** > **III** > **V**, whereas for **3S5S**, the stability order is **I** > **III** > **II** > **IV** > **V**. In summary, for **3S5O** and **3O5S**, the most stable tautomer is the oxo-thione form, **I**. Similarly, for **3S5S**, the dithione form **I** (see Scheme 1) is the most stable tautomer. On the other hand, as mentioned in the Introduction, the energy barriers connecting the tautomers are very high; therefore, we can safely assume that only the most stable structure in each case will exist in the gas phase. This reduces the possibility of gas-phase protonation to two sites: the carbonyl and thiocarbonyl groups in **3S5O** and **3O5S** and the two thiocarbonyl groups in **3S5S**. In other words, the direct protonation of these species would yield tautomers **1a**, **1b**, **2a**, or **2b** exclusively (see Figure 1).

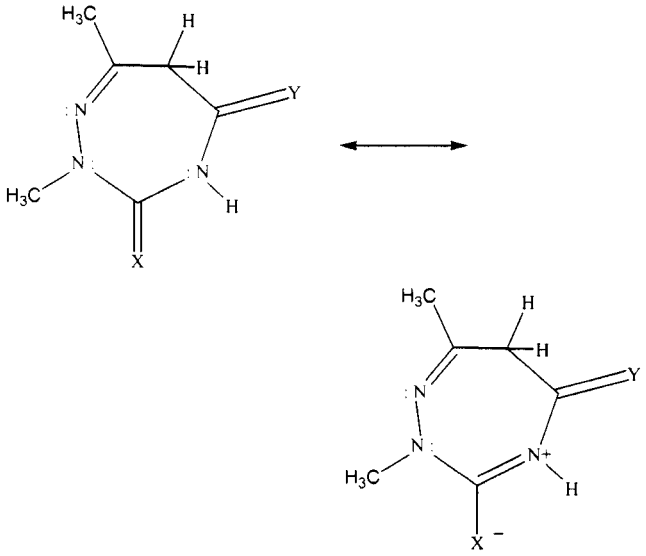
Our calculations show that when the heteroatom at position 3 is a sulfur atom its protonation to yield tautomers **2a** or **2b** is

TABLE 2: Total Energies[a] (*E*, hartrees), Zero-Point Energies[b] (ZPE, kcal mol^{-1}), and Relative Energies[c] (ΔE, kcal Mol^{-1}) for the Different Protonated Forms of the Thiotriazepines Investigated

protonated tautomer	3S5O			3O5S			3S5S		
	E	ZPE	ΔE	*E*	ZPE	ΔE	*E*	ZPE	ΔE
1a	−872.239406	0.169068	14.00	−872.248379	0.166128	6.09	−1195.201592	0.163811	9.91
1b	−872.238143	0.169005	14.75	−872.249149	0.166119	5.60	−1195.202715	0.163866	9.24
2a	−872.259126	0.166176	0.00	−872.250283	0.169196	6.61	−1195.211995	0.163897	3.43
2b	−872.258353	0.166375	0.60	−872.250442	0.169263	6.55	−1195.211282	0.164254	4.08
3a	−872.239516	0.165925	12.16	−872.240758	0.165692	10.63	−1195.200532	0.160439	8.69
3b	−872.239159	0.165723	12.28	−872.239090	0.165513	11.57	−1195.199973	0.160155	8.88
3c	−872.232528	0.165339	16.22	−872.240278	0.165735	10.95	−1195.199961	0.160388	9.02
3d	−872.231330	0.165067	16.82	−872.235719	0.165131	13.47	−1195.198851	0.160136	9.57
4a	−872.249450	0.166094	6.03	−872.255883	0.166291	1.47	−1195.212319	0.160627	1.40
4b	−872.257541	0.166303	1.07	−872.258225	0.166289	0.00	−1195.214540	0.160622	0.00
4c	−872.253113	0.166370	3.88	−872.248669	0.165938	5.80	−1195.210106	0.160754	2.86
4d	−872.244444	0.166105	9.17	−872.245778	0.165924	7.61	−1195.207566	0.160753	4.45

[a] Calculated at the B3LYp/6-311+G(3df,2p)//B3LYP/6-31G* level of theory. [b] Calculated at the B3LYP/6-31G* level of theory. [c] These values include the corresponding ZPE correction scaled by the empirical factor 0.9801.

SCHEME 2



systematically favored over the protonation at the heteroatom at position 5 to yield tautomers **1a** or **1b**. In contrast, **3O5S** protonates preferentially at the heteroatom at position 5. This implies that all the triazepines under investigation behave as sulfur bases in the gas phase, although the active center depends on the nature of the heteroatom in position 3. The enhanced basicity of the heteroatom attached to position 3, as has been suggested for the particular case of the thiouracil derivatives,[10] can be associated with the contribution of a zwiterionic configuration, $-^{+}N{=}C(-X^{-})-$, which accumulates negative charge at the heteroatom X (see Scheme 2).

This is confirmed by the NBO analysis of compound **3S5S**, which shows that the net charge on the sulfur at position 3 (−0.325) is much more negative than the net charge on the sulfur at position 5 (−0.153). Consistent with this result, the C=S bond length of the thiocarbonyl group attached at position 3 (1.674 Å) is longer than that of the thiocarbonyl group attached to position 5 (1.653 Å), in fairly good agreement with the X-ray results found in the crystal,[15] which yield 1.660 and 1.642 Å, respectively, for these two bond lengths. The fact that the oxygen atom at position 3 is not the most basic site for the particular case of the **3O5S** derivative can be understood if one takes into account that, in general, the intrinsic basicity of thiocarbonyl derivatives[19] is higher than those of the corresponding carbonyl analogues. Hence, **3O5S** should be a sulfur base, in agreement with our calculations. Nevertheless, the enhanced basicity of the heteroatom at position 3 is reflected in the fact that its intrinsic basicity is only 1 kcal mol^{-1} smaller than that of the sulfur atom at position 5, even though the normal gap between the intrinsic basicities of thiocarbonyl and carbonyl groups is much larger (≈10 kcal mol^{-1}).[19] It is worth mentioning that the same effect was found to be quantitatively higher for thiouracils[10] than for triazepines, and as a consequence, the increase in the intrinsic basicity of the oxygen atom at position 4 of the 2-thiouracil[10] was large enough to render the oxygen atom at position 4 more basic than the sulfur atom at position 2.

TABLE 3: Gas-Phase Proton Affinities (PA)[a] of Thiotriazepines Obtained at the B3LYP/6-311+G(3df,2p)// B3LYP/6-31G* Level of Theory

	3S5O	3O5S	3S5S
PA_{calcd}	215.2	206.8[b]−213.5[c]	214.3[b]−217.4[c]
PA_{expl}	213.8	211.3	215.2

[a] All values are in kcal/mol. [b] Values obtained assuming that protonated species are formed by a direct protonation of the neutral to yield conformer **2a**. [c] Values obtained assuming that the most stable conformer **4b** is formed by isomerization of species **2a**.

Hence, assuming that for the neutrals only the keto−thione tautomers will be present in the gas phase, protonation of triazepines would yield tautomer **2a** exclusively. Under this assumption, the estimated gas-phase proton affinities (PAs) are those summarized in Table 3. The first conspicuous fact is that although the PA of **3S5O** is in good agreement with the experimental value, those of **3O5S** and **3S5S**, in particular that of the former, underestimate the corresponding experimental measurements. Taking into account that, as indicated above, B3LYP/6-311+G(3df,2p) proton affinities usually overestimate the experimental values, the aforementioned results seem to indicate that for the latter two compounds a different (more stable) protonated species is being observed in the FTICR experiments.

Indeed, our theoretical survey on the relative stability of the various protonated tautomers indicates that whereas for **3S5O** the tautomer **2a** produced by a direct protonation of the corresponding neutral is the global minimum of the PES this is not the case for the other two derivatives. As illustrated in Figure 2, and as can be deduced from the values in Table 2, for **3O5S** and **3S5S**, the global minimum **4b** corresponds to the enol−enethiol and to the enethiol−enethiol tautomers, respectively. It can be also observed that the remaining tautomeric forms, although they are local minima of the PES, lie higher in energy. More important is that, if one assumes that tautomer **4b** is

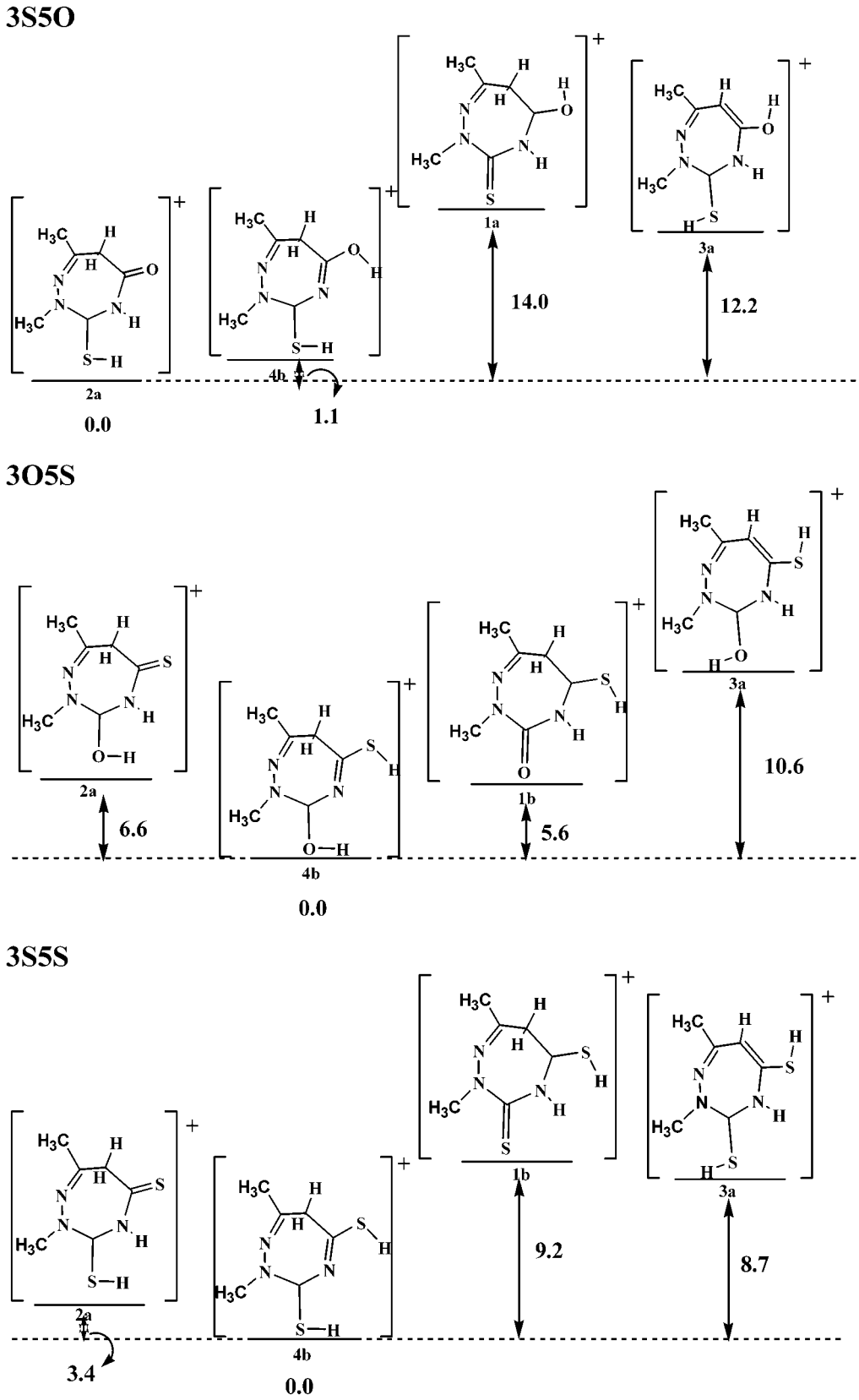


Figure 2. Relative stability of the different protonated structures of thiotriazepines. All values are in kcal mol^{-1}.

produced when **3O5S** and **3S5S** become protonated in the gas phase, the calculated proton affinities are in better agreement with the experimental values (see Table 3) than if the protonation yields the **2a** tautomer.

Because tautomer **4b** cannot be produced by a direct protonation of the corresponding neutrals, it must arise from a tautomerization, through a 1,3-H shift, of structures **2** or **1**, the only ones that can be formed by a direct protonation of the neutrals. However, as illustrated in Figure 3a−c, the activation barriers connecting the various tautomers are quite high, ranging from 17.5−35 kcal mol^{-1}; therefore, they cannot be surpassed under normal experimental conditions.

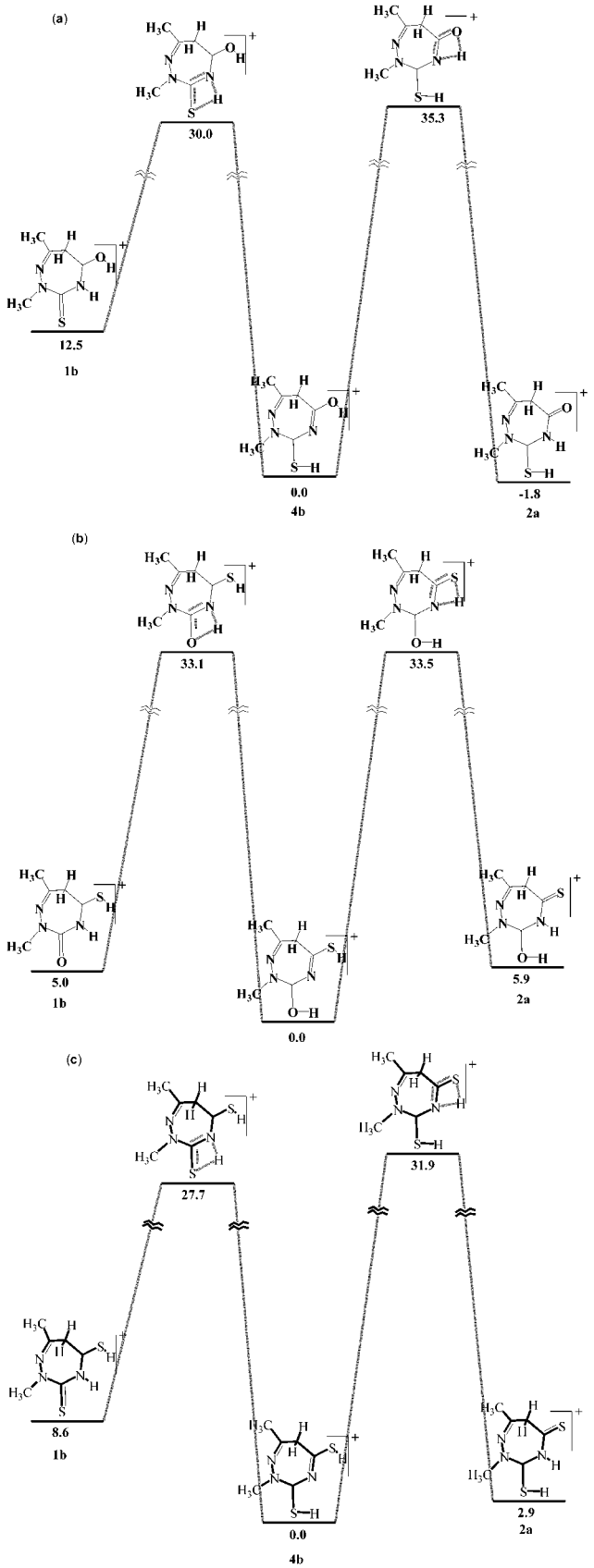


Figure 3. Prototropic tautomerization barriers between the relevant protonated forms of triazepines: (a) protonated forms of **3S5O**; (b) protonated forms of **3O5S**; and (c) protonated forms of **3S5S**.

Hence, we must assume that the **2a** → **4b** tautomerization must proceed through a mechanism similar to that proposed elsewhere[10] to explain the gas-phase basicity of thiouracils,

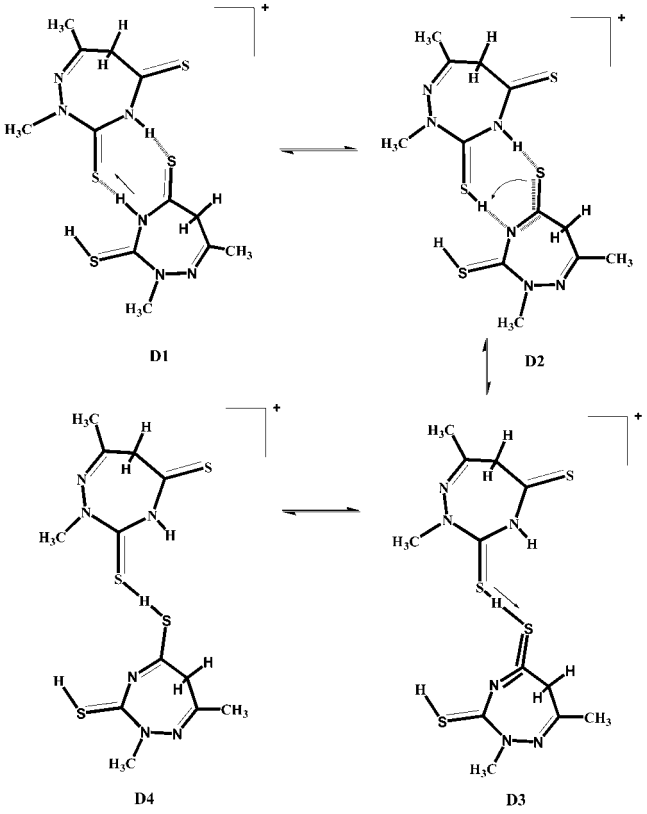


Figure 4. Proposed mechanism to explain the formation of the most stable protonated form of thiotriazepines that cannot be produced by direct protonation of the neutral species.

which involves the formation of hydrogen-bonded clusters between the corresponding neutral and the protonated tautomer **2a** (or **1b**). The main steps of this mechanism are shown in Figure 4 for the particular case of the dithio derivative. After the formation of the dimer **D1** between the neutral and the protonated structure **2a**, in which the proton is attached to the sulfur atom in position 3, there is a proton transfer (indicated by an arrow) from the N−H group of the protonated moiety to the thiocarbonyl group of the neutral to yield a new hydrogen-bonded complex **D2**. An in-plane rotation of the neutral moiety leads to a new hydrogen-bonded complex **D3** in which the N−H···S and the S−H···N hydrogen bonds are replaced by a S−H···S hydrogen bond. A subsequent proton transfer along this hydrogen bond would yield complex **D4**, which formally corresponds to a complex between the neutral triazepine and the most stable dienethiol protonated species, **4b**. In light of the remarkable similarity between thiouracils and thiotriazepines, it can be reasonably expected that, as it has been shown for the former, the activation barriers associated with all these steps will lie lower in energy than the noninteracting systems, reflecting the significant stability (≈20 kcal mol^{-1}) of the mixed dimers between neutral and protonated forms. This would imply that the formation of these dimers would lead from **2a** to **4b** protonated species in an overall exothermic process. Of course, other alternative mechanisms via complexes with the probe reagent are also possible, as suggested recently by Kurinovich and Lee[54] in a study of the acidity of uracil, but this calls for a separate study.

Conclusions

Our theoretical calculations indicate that, in contrast with thiouracils,[10] where the 2-thio derivative was predicted to be an oxygen base, the 3-thio-5-oxo (**3S5O**), 5-thio-3-oxo (**3O5S**),

and 3,5-dithio (**3S5S**) derivatives of 2,7-dimethyl-[1,2,4]-triazepine behave as sulfur bases in the gas phase. However, a comparison between calculated and FTICR experimental proton affinities clearly suggests that for the particular case of **3O5S** and **3S5S** an evolution from tautomers **1** or **2**, produced by the direct protonation of the neutrals, toward the most stable tautomer, **4b**, must take place. Because the tautomerization barriers are very high, the corresponding 1,3-H shifts cannot occur under normal experimental conditions. Hence, one must assume that this tautomerization takes place through the formation of hydrogen-bonded complexes between the neutral and protonated forms, for which the necessary hydrogen shifts involve barriers that are lower in energy than those for the noninteracting systems. Thus, if the aforementioned mixed dimers are formed, the **2a** → **4b** tautomerization process is energetically accessible.

Acknowledgment. This work has been partially supported by the DCIT, projects nos. BQU2000-0245 and BQU2000-1497, and by the Acción Integrada between the Departments of Chemistry of the Universidad Autónoma de Madrid and the Université Caddi Ayad de Marrakech. A generous allocation of computational time at the CCC of the Universidad Autónoma de Madrid is also gratefully acknowledged.

References and Notes

(1) Kebarle, P. In *Techniques for the Study of Ion−Molecule Reactions*; Farrar, J. M., Saunders, J. W., Eds.; Wiley & Sons: New Yotk, 1988; Chapter 5.

(2) Laukien, F. H.; Allemann, M.; Bischofberger, P.; Grossmann, P.; Kellerhals, H. P.; Kofel, P. In *Fourier Transfrom Mass Spectrometry: Evolution, Innovation, and Applications*; Buchanan, M. V., Ed.; American Chemical Society: Washington, DC, 1987.

(3) Harrison, A. G. *Mass Spectrom. Rev.* **1997**, *16*, 201.

(4) Raczynska, E. D.; Decouzon, M.; Gal, J.-F.; Maria, P.-C.; Wozniak, K.; Kurg, R.; Carins, S. N. *Trends Org. Chem.* **1998**, *7*, 95.

(5) Abboud, J.-L. M.; Notario, R. In *Energetics of Stable Molecules and Reactive Intermediates*; Minas da Piedade, M. E., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1999.

(6) Marino, T.; Russo, N.; Sicilia, E.; Toscano, M. *Adv. Quantum Chem.* **1999**, *36*, 93.

(7) Hunter, E. P.; Lias, S. G. *Proton Affinity Evaluation.* In NIST Chemistry Web Book, NIST Standard References Database Number 69. (http://webbookk.nist-gov); National Institute of Standards and Technology: 2002.

(8) Aubry, C.; Holmes, J. L. *Int. J. Mass Spectrom.* **2000**, *200*, 277.

(9) Gal, J.-F.; Maria, P.-C.; Raczynska, E. D. *J. Mass Spectrom.* **2001**, *36*, 699.

(10) Lamsabhi, M.; Alcami, M.; Mo, O.; Bouab, W.; Esseffar, M.; Abboud, J. L. M.; Yanez, M. *J. Phys. Chem. A* **2000**, *104*, 5122.

(11) Bartsh, H.; Erker, T. *J. Heterocycl. Chem.* **1988**, *25*, 1151.

(12) Bellantuono, C.; Reggi, G.; Tognoni, G.; Grattini, S. *Drugs* **1980**, *19*, 195.

(13) Hasnaoui, A.; Lavergne, J.-P.; Villefont, P. *J. Heterocycl. Chem.* **1978**, *15*, 71.

(14) Hasnaoui, A.; Lavergne, J.-P.; Villefont, P. *Org. Mass Spectrom.* **1978**, *13*, 353.

(15) Toledano, P.; Itto, M. Y. A.; Hasnaoui, A. *Acta Crystallogr., Sect. C* **1995**, *51*, 2066.

(16) Simeonov, M. F.; Fueloep, F.; Sillanpaeae, R.; Pihlaja, K. *J. Org. Chem.* **1997**, *62*, 5089.

(17) Pihlaja, K.; Simeonov, M. F.; Fueloep, F. *J. Org. Chem.* **1997**, *62*, 5080.

(18) Aitali, M.; Ait-Itto, M. Y.; Hasnaoui, A.; Riahi, A.; Karim, A.; Garcia-Grada, S.; Gutierrez-Rodriguez, A. *Acta Crystallogr., Sect. C* **2000**, *56*, e315.

(19) Abboud, J. L. M.; Mo, O.; de Paz, J. L. G.; Yanez, M.; Esseffar, M.; Bouab, W.; El-Mouhtadi, M.; Mokhlisse, R.; Ballesteros, E.; Herreros, M.; Homan, H.; Lopez-Mardomingo, C.; Notario, R. *J. Am. Chem. Soc.* **1993**, *115*, 12468.

(20) Molina, M. T.; Yanez, M.; Mo, O.; Notario, R.; Abboud, J. L. M. In *The Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed.; Wiley & Sons: Chichester, U.K., 1997; Vol. 3, p 1355.

(21) Katritzky, A. R.; Szafran, M.; Stevens, J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1507.

(22) Les, A.; Adamowicz, L. *J. Am. Chem. Soc.* **1990**, *112*, 1504.

(23) Leszczynski, J.; Lammertsma, K. *J. Phys. Chem.* **1991**, *95*, 3128.

(24) Leszczynski, J. *J. Phys. Chem.* **1992**, *96*, 1649.

(25) Rubin, Y. V.; Morozov, Y.; Venkateswarlu, D.; Leszczynski, J. *J. Phys. Chem. A* **1998**, *102*, 2194.

(26) Lamsabhi, A. M.; El Messaoudi, T.; Esseffar, M.; Alcamí, M.; Yáñez, M. *New J. Chem.* **2002**, *26*, 711.

(27) Lehman, T. A.; Bursey, M. M. *Ion Cyclotron Resonance Spectrometry*; Wiley & Sons: New York, 1976.

(28) Marshall, A. G.; Hendrickson, L.; Jackson, G. S. *Mass Spectrom. Rev.* **1998**, *17*, 1.

(29) *FT-ICR/MS Analytical Applications of Fourier Transform Ion Cyclotron Resonance Mass Specrometry*; Asamoto, B., Ed.; VCH Publichers: New York, 1991.

(30) Loss, G.; Hessler, W.; Barth, A. *Chem. Ber.* **1985**, *91*, 150.

(31) Hasnaoui, A.; Messaoudi, M. E.; Lavergne, J.-P. *J. Heterocycl. Chem.* **1985**, *22*, 25.

(32) Hasnaoui, A.; Messaoudi, M. E.; Lavergne, J.-P. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 129.

(33) Messaoudi, M. E.; Hasnaoui, A.; Mouhtadi, M. E.; Lavergne, J.-P. *Bull. Soc. Chim. Belg.* **1992**, *10*, 977.

(34) Abboud, J. L. M.; Cabildo, P.; Canada, T.; Catalan, J.; Claramunt, R. M.; de Paz, J. L. G.; Elguero, J.; Homan, H. *J. Org. Chem.* **1992**, *57*, 3938.

(35) Bartmess, J. E.; Giorgiadis, R. M. *Vacuum* **1983**, *3*, 149.

(36) Miller, K. J. *J. Am. Chem. Soc.* **1990**, *112*, 8533.

(37) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.3; Gaussian, Inc.: Pittsburgh, PA, 1998.

(38) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(39) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.

(40) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(41) Bauschlicher, C. W. *Chem. Phys. Lett.* **1995**, *246*, 40.

(42) Llamas-Saiz, A. L.; Foces-Foces, C.; Mo, O.; Yanez, M.; Elguero, E.; Elguero, J. *J. Comput. Chem.* **1995**, *16*, 263.

(43) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **2001**, *114*, 108.

(44) Hu, Z.; Boyd, R. J. *J. Chem. Phys.* **2000**, *113*, 9393.

(45) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

(46) Wong, M. W. *Chem. Phys. Lett.* **1996**, *256*, 391.

(47) Smith, B. J.; Radom, L. *Chem. Phys. Lett.* **1994**, *231*, 345.

(48) Amekraz, B.; Tortajada, J.; Morizur, J. P.; Gonzalez, A. I.; Mo, O.; Yanez, M.; Leito, I.; Maria, P. C.; Gal, J. F. *New J. Chem.* **1996**, *20*, 1011.

(49) Burk, P.; Koppel, I. A.; Koppel, I.; Leito, I.; Travnikova, O. *Chem. Phys. Lett.* **2000**, *323*, 482.

(50) Bouchoux, G.; Gal, J. F.; Maria, P. C.; Szulejko, J. E.; McMahon, T. B.; Tortajada, J.; Luna, A.; Yanez, M.; Mo, O. *J. Phys. Chem. A* **1998**, *102*, 9183.

(51) Bouchoux, G.; Defaye, D.; McMahon, T.; Likholyot, A.; Mó, O.; Yáñez, M. *Chem.−Eur. J.* **2002**, *8*, 2900.

(52) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

(53) Reed, A.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735.

(54) Kurinovich, M. A.; Lee, J. K. *J. Am. Chem. Soc.* **2000**, *112*, 6258.