Prototropic tautomerism of 3,5-(oxo/thioxo) derivatives of 2,7-dimethyl-1,2,4-triazepines†

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The relative stability of the different tautomers of the 3-thio-5-oxo, 5-thio-3-oxo, 3,5-dioxo and 3,5-dithio derivatives of 2,7-dimethyl-1,2,4-triazepine has been studied through the use of density functional theory (DFT) methods. The structure and vibrational frequencies of all the stable tautomers and all the transition states connecting them have been calculated at the B3LYP/6-31G* level of theory. Final energies have been obtained in single-point B3LYP/6-311+G(3df,2p) calculations. In all the cases the most stable conformer is the oxo-thione, the dioxo or the dithione form, while the mercapto-oxo tautomers are the second more stable structures. This behavior resembles closely that reported in the literature for uracil and its thio derivatives. As for uracil and thio-uracil derivatives, the tautomerism activation barriers are high enough as to conclude that only the oxo-thione structures should be found in the gas phase. The relative stabilities should change, however, in aqueous solution because the corresponding prototropic tautomerisms are accompanied by significant changes in the dipole moment of the system. The ionization of 1,2,4-triazepines involves bonding changes that are consistent with the unimolecular fragmentations observed in their mass spectra. The bonding characteristics of the carbonyl and thiocarbonyl groups depend on their relative positions. When these groups are attached to the carbon between two N atoms, the linkage is weaker than when they are attached to the carbon between C and N atoms. This is clearly reflected in the molecular force field and should be easily detected in the corresponding infrared spectrum, as well as in the reactivitiy of these systems in the gas phase.

Heterocyclic compounds have found widespread application as useful reaction intermediates in organic synthesis.[1,2] They are also good ligands that form stable and useful complexes with transition metals.[3–5] Furthermore, some of them are active drugs with important applications in pharmacology.[6–10] In particular, it has been shown that heterocycles attached to seven-membered rings exhibit important biochemical activity.[6–8] For this reason the different oxo and thio derivatives of diazepines and triazepines have attracted a great deal of attention[11–15] as starting material in the synthesis of fused heterocyclic systems with potential pharmacological activity.

In spite of the efforts devoted to the synthesis of these kinds of compounds, very little is known about the structures, relative stability or intrinsic reactivity of triazepines. In fact, we are only aware of some mass spectrometry studies on the unimolecular fragmentation of 1,2,4-triazepines,[16,11] the X-ray diffraction determination of the structure of some 1,2,4-triazepine and 1,3,4-triazepine derivatives[17–19] and the complexes formed by 1,2,4-triazepines with ruthenium(II).[20] To gain some insight on these aspects of triazepine chemistry we have considered it of interest to carry out a systematic theoretical study of the structure and relative stability of 1,2,4-triazepines. We have focused our attention on the 3-thio-5-oxo, 5-thio-3-oxo, 3,5-dioxo and 3,5-dithio derivatives of 2,7-dimethyl-1,2,4-triazepine because these derivatives present a remarkable resemblance with uracil and thiouracil derivatives, which besides their biological importance, exhibit a quite peculiar and interesting gas-phase reactivity strongly influenced by possible prototropic tautomerisms.[21]

As uracil and thiouracil derivatives the 1,2,4-triazepines under investigation may exhibit five different tautomeric forms with different conformations. Therefore, one of the aims of our paper is not only to estimate the relative stability of the different tautomeric forms, but also the height of the barriers connecting them. For this purpose we have carried out extensive density functional theory (DFT) calculations on the corresponding potential energy surfaces (PES). In the last decade, *ab initio* and DFT methods have provided an efficient and reliable tool for the determination of molecular structures and stabilities. Actually, our knowledge on the prototropic equilibria of uracil and thiouracil derivatives is essentially of theoretical origin,[22–27] or the result of using combined experimental and theoretical information.[21,28,29]

Computational details

As indicated above, we have considered the five different tautomeric forms of 2,7-dimethyl-3-thio-5-oxo-1,2,4-triazepine (**3S5O**), 2,7-dimethyl-3-oxo-5-thio-1,2,4-triazepine (**3O5S**), 2,7-dimethyl-3,5-dioxo-1,2,4-triazepine (**3O5O**) and 2,7-dimethyl-3,5-dithio-1,2,4-triazepine (**3S5S**) represented in Fig. 1. In all cases the different conformers of each tautomer were considered, including the rotational conformation of the

† Electronic supplementary information (ESI) available: the B3LYP/6-31G* optimized geometries of all the structures included in Fig. 1 and the corresponding TS. See http://www.rsc.org/suppdata/nj/b1/b109397e/

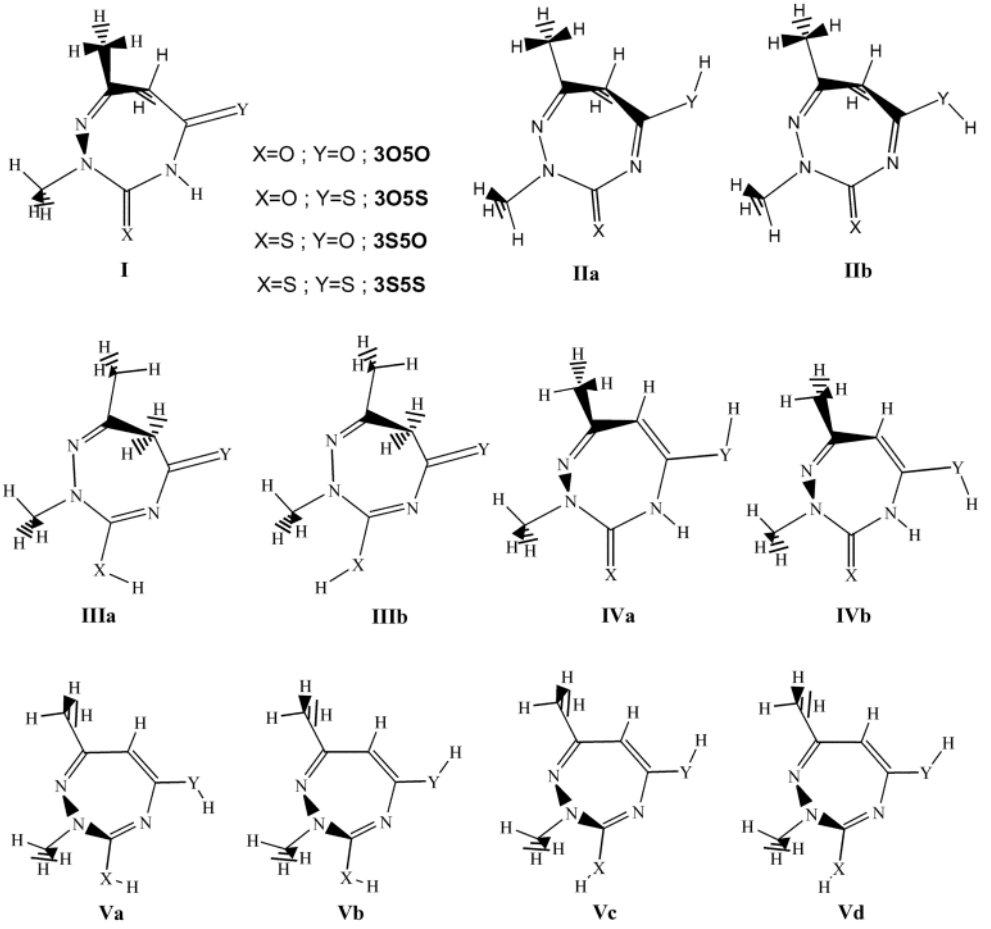


Fig. 1 Different tautomeric forms of neutral 3,5-(oxo/thioxo) 2,7-dimethyl-1,2,4-triazepine derivatives.

methyl groups, but only the structures corresponding to the most stable methyl group conformation were considered in our discussion for the sake of conciseness, so that for each compound eleven different structures are reported. The geometries of these forty-four different forms have been optimized at the B3LYP/6-31G* level. The corresponding harmonic vibrational frequencies were evaluated at the same level of theory to verify that all structures found corresponded to local minima of the PES and to estimate the corresponding zero point energy (ZPE) corrections, which were scaled by the empirical factor 0.9806.[30] A similar procedure was adopted to locate the transition states (TS) associated with prototropic tautomerization processes. The TSs have been named by indicating the two minima that they connect.

The B3LYP hybrid functional includes the Becke three-parameter exchange potential[31] with the nonlocal correlation functional of Lee, Yang and Parr[32] and it has been proved to be quite reliable to describe both geometries and harmonic vibrational frequencies.

In order to obtain more reliable energies of both local minima and transition states we have performed single point energy calculations at the B3LYP/6-311+G(3df,2p) level. It has been shown that this approach is quite well suited for the study of these kinds of prototropic tautomerisms,[21] yielding relative energies in excellent agreement with those obtained through the use of high-level *ab initio* techniques such as G2 theory.[33] Therefore, we can safely expect that the errors on these energies will be of the order of 1 kcal mol^{-1}.

Net atomic charges of the most stable tautomers were obtained by using the natural bond orbital (NBO) approach.[34] The bonding characteristics were analyzed by means of the atoms in molecules (AIM) theory of Bader.[35] For this purpose we have located the relevant bond critical points and evaluated the charge density and the energy density at each of them. All DFT calculations have been carried out using the Gaussian 98 series of programs.[36] To perform the AIM analysis we have used the AIMPAC series of programs.[37]

Results and discussion

The B3LYP/6-311+G(3df,2p) total energies, as well as the ZPE corrections obtained at the B3LYP/6-31G* level, for all the stable isomers and TSs under study are given in Table 1. The first conspicuous fact is that the tautomer **I** is the most stable one for the four triazepine derivatives, in accordance with the assumptions of Hasnaoui *et al.*[16]

Structure and bonding

For the sake of conciseness we will discuss only the structures of tautomers **I**, which are schematized in Fig. 2. The optimized geometries of all the other structures are given as supporting information.

From the optimized geometrical parameters given in Fig. 2 it can be observed that for the four compounds, the C7–N1–N2 fragment of the seven-membered ring of the triazepine exhibits almost identical characteristics, in terms of bond lengths, bond angles and charge densities at the bond critical points (see Table 2). This clearly indicates that substituent effects in triazepines are local and that they are not transmitted to the positions not directly bonded to the substituent. As expected, the structural characteristics of the rest of the ring are quite sensitive to the nature of the substituents at a given position (C3 or C5), but almost independent of the nature of the other substituent. For example, the N4–C5(S)–C6 [or N4–C5(O)–C6] fragment in the **3O5S** (or **3O5O**) compound is rather

Table 1 B3LYP/6-311+G(3df,2p) total energies (hartrees), ZPE corrections (hartrees) evaluated at the B3LYP/6-31G(d) level, relative energies (ΔE, kcal mol^{-1}), relative free energies (ΔG, kcal mol^{-1}) with respect the most stable tautomer, and dipole moments (μ in Debyes). ΔE and ΔG include the scaled ZPE corrections

	3O5O					**3S5O**					**3O5S**					**3S5S**				
	Energy	ZPE	ΔE	ΔG	μ	Energy	ZPE	ΔE	ΔG	μ	Energy	ZPE	ΔE	ΔG	μ	Energy	ZPE	ΔE	ΔG	μ
I	−548.95825	0.15692	0.0	0.0	3.7	−871.90919	0.15731	0.0	0.0	4.8	−871.91120	0.15740	0.0	0.0	3.8	−1194.86362	0.15516	0.0	0.0	4.6
IIa	−548.92151	0.15842	22.3	22.2	6.9	−871.87298	0.15607	22.0	21.9	7.7	−871.88523	0.15300	13.6	13.2	6.0	−1194.83771	0.15067	13.5	13.2	6.7
IIb	−548.93214	0.15893	16.0	15.8	4.7	−871.88372	0.15662	15.6	15.6	5.6	−871.88808	0.15315	11.9	11.6	4.6	−1194.84065	0.15078	11.7	11.5	5.5
IIIa	−548.93133	0.15895	16.5	16.5	4.7	−871.88430	0.15313	13.0	12.8	5.0	−871.88474	0.15671	16.2	16.2	5.4	−1194.83818	0.15093	13.4	13.1	5.7
IIIb	−548.91695	0.15817	25.0	25.0	7.1	−871.87849	0.15296	16.6	16.2	6.4	−871.87090	0.15584	24.3	24.1	7.7	−1194.83225	0.15084	17.0	16.8	7.0
IVa	−548.93167	0.15885	16.2	16.2	4.6	−871.88148	0.15647	16.9	16.7	5.5	−871.89330	0.15337	8.7	8.5	3.9	−1194.84452	0.15101	9.4	9.0	4.9
IVb	−548.92723	0.15831	18.7	18.5	2.5	−871.87859	0.15609	18.4	18.2	3.2	−871.89410	0.15335	8.2	8.0	2.6	−1194.84565	0.15103	8.7	8.3	3.6
Va	−548.91212	0.15855	28.3	28.5	1.5	−871.86617	0.15259	24.1	24.0	0.8	−871.87082	0.15265	22.4	22.1	0.8	−1194.82540	0.14688	18.9	18.5	0.2
Vb	−548.90706	0.15849	31.4	31.3	1.3	−871.86088	0.15206	27.1	27.3	1.9	−871.87030	0.15300	23.0	23.0	0.8	−1194.82475	0.14712	19.4	19.2	1.4
Vc	−548.89726	0.15807	37.3	37.6	2.9	−871.85823	0.15249	29.0	29.0	2.7	−871.86075	0.15255	28.7	28.8	3.1	−1194.82252	0.14702	20.8	20.5	2.5
Vd	−548.90363	0.15822	33.4	33.7	2.3	−871.86441	0.15263	25.2	25.1	1.5	−871.86210	0.15234	27.7	27.7	2.6	−1194.82320	0.14686	20.3	19.8	1.7
TS I-IIb	−548.88120	0.15391	44.8	44.9	4.8	−871.83226	0.15147	44.7	44.6	5.8	−871.83236	0.15034	45.1	45.1	5.8	−1194.79761	0.14794	37.0	36.9	5.6
TS I-IIIa	−548.88936	0.15426	39.9	40.0	4.8	−871.85181	0.15037	31.7	31.6	5.1	−871.84256	0.15193	39.7	39.7	5.1	−1194.80633	0.14813	31.6	31.4	5.4
TS I-IVa	−548.85605	0.15307	60.1	60.0	2.2	−871.80826	0.15073	59.3	58.9	3.3	−871.82317	0.14992	50.6	50.5	2.6	−1194.75189	0.14741	65.3	65.4	2.2
TS IIIa-Vb	−548.83617	0.15264	72.3	72.5	2.7	−871.78874	0.14663	69.0	68.4	3.8	−871.78454	0.14923	74.5	74.6	3.6	−1194.73866	0.14349	71.2	71.2	4.0
TS IVa-IVb	−548.92480	0.15798	20.0	20.2	2.5	−871.87263	0.15518	21.6	21.5	4.5	−871.88936	0.15284	10.9	10.8	3.4	−1194.84158	0.15049	11.0	10.8	4.3
TS IVb-Va	−548.86655	0.15349	53.8	53.8	0.6	−871.82901	0.14956	45.5	45.3	0.9	−871.82761	0.14781	46.6	46.2	1.1	−1194.79000	0.14395	39.3	38.7	1.6
TS Vb-Va	−548.89808	0.15710	36.2	36.6	1.6	−871.85263	0.15119	31.7	31.8	1.8	−871.86309	0.15214	27.0	27.2	1.1	−1194.81774	0.14621	23.3	23.2	1.4

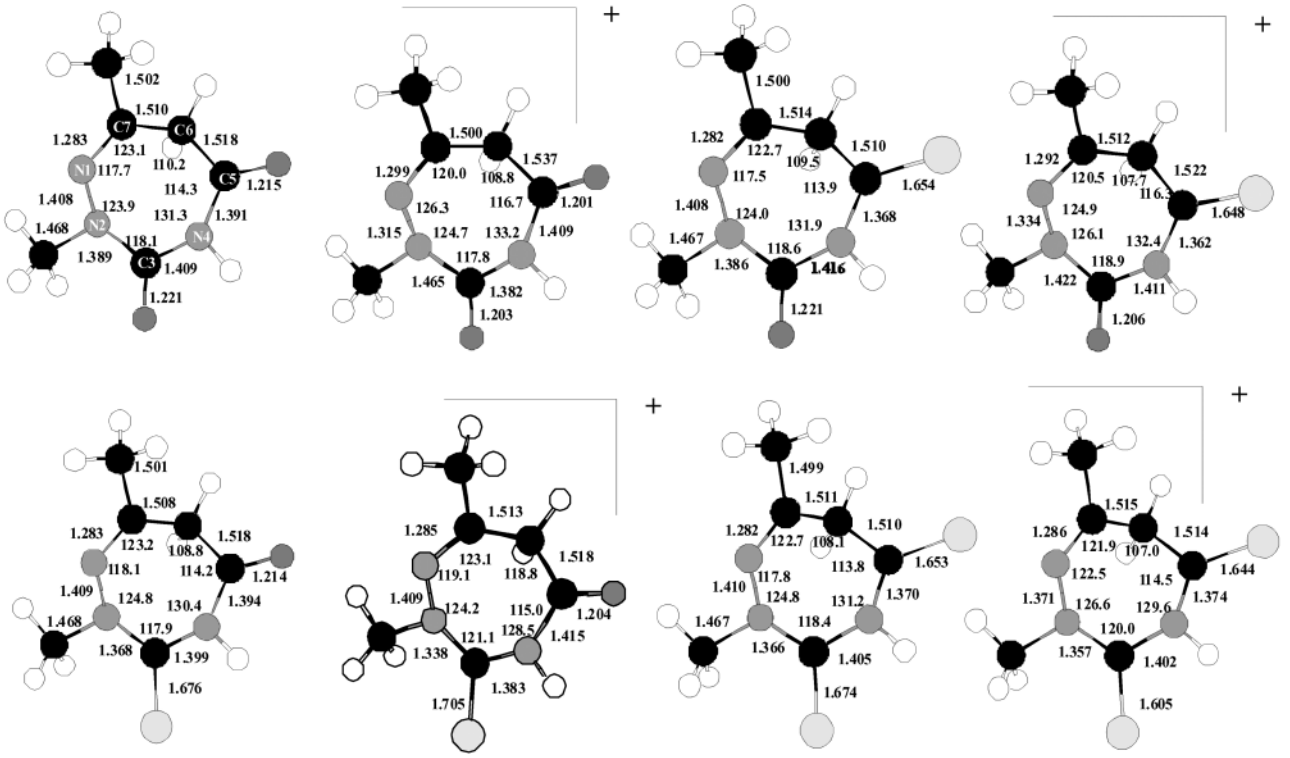


Fig. 2 B3LYP/6-31G* optimized geometries of tautomer **I** of 3,5-(oxo/thioxo) 2,7-dimethyl-1,2,4-triazepine derivatives and the corresponding radical cations. Bond lengths are in Å and bond angles in degrees.

similar to that of the **3S5S** (or **3S5O**) derivative, even though in the latter the nature of the substituent at C3 is different. The same is true if one considers the N2–C3(S)–N4 [or N2–C3(O)–N4] fragments in **3S5O** and **3S5S** (or **3O5S** and **3O5O**). It can be also observed that the N2–C3 and the C3–N4 bond distances are longer for the 3-oxo than for the 3-thio derivatives. A similar trend is found when the N4–C5 and C5–C6 bond lengths of the 5-oxo derivatives are compared with those of the 5-thio derivatives. Since oxygen is more electronegative than sulfur, the carbonyl group depopulates the bonds to which it is attached to a greater degree, as illustrated by the values of the charge densities at the corresponding bond critical points (see Table 2).

It is also worth noting that the intrinsic characteristics of the carbonyl or the thiocarbonyl groups change slightly depending on their relative position within the ring. When they are attached at C3, the corresponding C=O (or C=S) bond is weaker as reflected in a smaller charge density at the bond critical point (see Table 2) and in a greater bond length. Consistently, the corresponding stretching frequency appears red-shifted. Indeed, while for the **3S5O** derivative the C=O stretching mode has a frequency of 1825 cm^{-1}, for **3O5S** the same band is predicted to be at 1784 cm^{-1} (see Table 3). Similarly, while for the former the C=S stretching frequency is estimated to be 1128 cm^{-1}, for the latter it is calculated to be 1233 cm^{-1}. This can been explained by considering the resonant structures depicted in Scheme 1. There are two resonant structures that imply the delocalization of a negative charge in the heteratom in position 3 and only one that delocalizes the charge in position 5. Furthermore, the former should be stabilized by the presence of an adjacent methyl group. Quite obviously, these differences should be reflected in their intrinsic reactivity and *a priori* one should expect the carbonyl or the thiocarbonyl group at C3 to be more basic than the carbonyl or the thiocarbonyl at C5. This is in contrast with what has been found recently for thiouracils, where the basicity of the carbonyl (or thiocarbonyl) attached at C2 (position similar to C3 in triazepines) is lower than that of the carbonyl (or thiocarbonyl) attached at C4 (position similar to C5 in triazepines).

Table 2 Charge density (ρ) and energy density [$H(\mathbf{r})$] at the bond critical points of tautomer **I** of 1,2,4-triazepines. Values within parentheses correspond to the radical cations

Bond	**3O5O**		**3S5O**		**3O5S**		**3S5S**	
	ρ / a.u.	$H(\mathbf{r})$ / a.u.	ρ / a.u.	$H(\mathbf{r})$ / a.u.	ρ / a.u.	$H(\mathbf{r})$ / a.u.	ρ / a.u.	$H(\mathbf{r})$ / a.u.
N1–N2	0.321 (0.393)	−0.297 (−0.416)	0.320 (0.345)	−0.295 (−0.338)	0.321 (0.376)	−0.297 (−0.386)	0.320 (0.347)	−0.294 (−0.338)
N2–C3	0.313 (0.266)	−0.435 (−0.305)	0.320 (0.326)	−0.496 (−0.426)	0.316 (0.292)	−0.444 (−0.374)	0.320 (0.325)	−0.498 (−0.517)
C3–N4	0.298 (0.315)	−0.398 (−0.440)	0.301 (0.322)	−0.420 (−0.471)	0.293 (0.296)	−0.384 (−0.388)	0.297 (0.300)	−0.411 (−0.406)
N4–C5	0.304 (0.291)	−0.445 (−0.404)	0.303 (0.277)	−0.437 (−0.371)	0.314 (0.318)	−0.496 (−0.504)	0.312 (0.309)	−0.491 (−0.479)
C5–C6	0.255 (0.242)	−0.212 (−0.195)	0.255 (0.252)	−0.212 (−0.210)	0.256 (0.246)	−0.214 (−0.202)	0.256 (0.250)	−0.214 (−0.209)
C6–C7	0.254 (0.258)	−0.210 (−0.221)	0.256 (0.256)	−0.212 (−0.213)	0.253 (0.253)	−0.208 (−0.208)	0.254 (0.252)	−0.210 (−0.207)
C7–N1	0.378 (0.356)	−0.656 (−0.605)	0.378 (0.369)	−0.656 (−0.635)	0.378 (0.361)	−0.657 (−0.617)	0.378 (0.369)	−0.657 (−0.635)
C3=X (O, S)	0.409 (0.425)	−0.709 (−0.738)	0.211 (0.217)	−0.248 (−0.226)	0.410 (0.422)	−0.709 (−0.735)	0.211 (0.214)	−0.249 (−0.256)
C5=X (O, S)	0.412 (0.424)	−0.705 (−0.729)	0.412 (0.425)	−0.706 (−0.731)	0.220 (0.226)	−0.264 (−0.277)	0.220 (0.227)	−0.264 (−0.277)

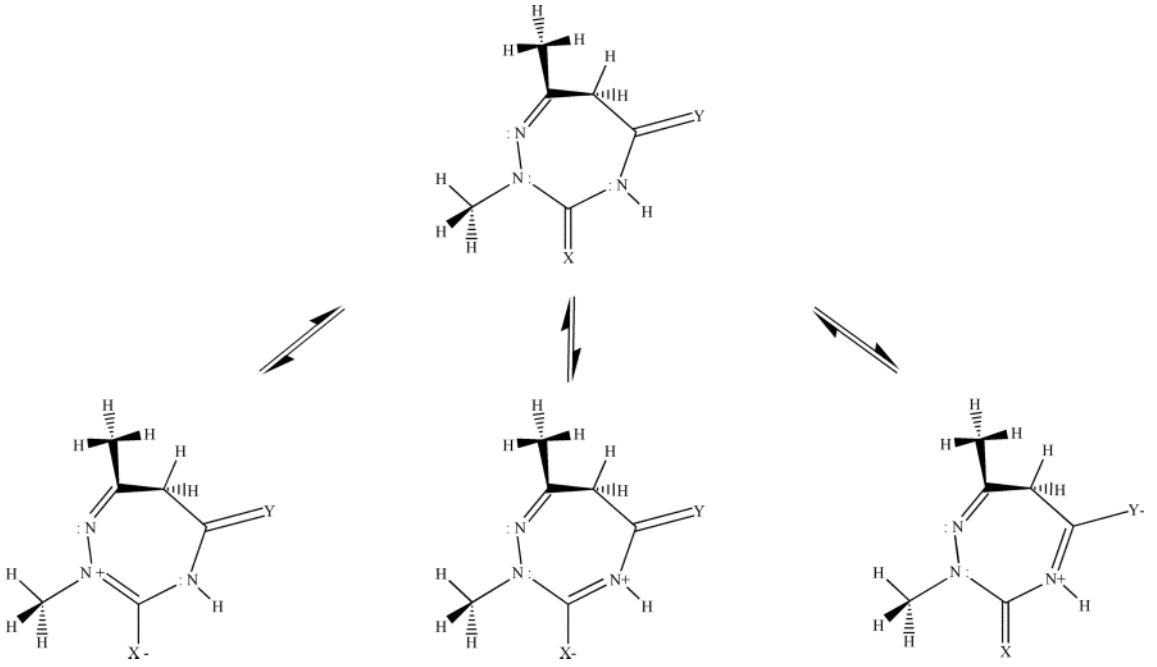
Table 3 Harmonic vibrational frequencies (v/cm^{-1}) and infrared intensities (I) of 1,2,4-triazepines

	3O5O		**3S5O**		**3O5S**		**3S5S**	
Assignment	v	I	v	I	v	I	v	I
Ring def.	82	0.3	65	0.6	68	0.4	63	0.4
CH_3 torsion	114	0.2	108	2.4	100	1.5	89	2.1
					113	0.7		
Ring def.	115	2.8	130	0.5	136	1.1	125	0.4
	139	0.7	158	0.7			163	4.3
CH_3 torsion	168	4.3	164	3.9	170	5.0	171	0.2
	201	0.3	201	0.2	201	0.1	201	0.5
C=S bending			286	11.3	287	7.2	249	9.4
Ring def.	297	1.0	306	0.4	295	4.1	302	1.0
	333	14.6	337	8.0	323	17.5	327	10.6
	357	14.3	362	9.4	363	6.3	339	1.5
	381	6.1	387	1.4	377	3.0	365	6.9
	408	8.8			415	1.8	392	5.1
							453	4.7
							481	7.5
C–O bending	427	7.9	411	8.4	488	12.3		
Ring def.	512	9.6	490	3.7	524	11.4	583	5.0
	557	4.0	514	14.1	595	7.5	642	10.2
	589	15.7	577	5.5				
C5–pyramid.	631	7.3	634	5.2	558	3.8	541	3.8
Ring def.	695	23.3	645	8.5	694	6.7	773	13.9
C3–pyramid.	727	7.1	621	1.4	711	2.5	623	0.7
N–H inversion	759	86.8	742	87.2	756	71.8	762	78.0
Ring def.	820	14.9	811	9.0	809	36.3	845	12.4
C6–C7 stretch.	877	7.3	872	4.2	862	2.3	864	11.0
C5–C6 stretch.	915	5.6	899	6.9	867	39.5	1051	25.9
N1–N2 stretch.	1014	17.8	961	20.1	1010	19.6	958	6.6
CH_3 rocking and twisting	968	4.4	975	4.8	962	1.9	966	12.3
	1070	3.4	1065	15.0	1055	22.6	1068	4.6
	1065	14.6	1069	3.0	1069	5.7		
					1132	35.2		
C5=S stretch.					1233	42.2	1276	4.2
C3=S stretch.			1128	129.2			1116	179.2
CH_3 rocking and twisting	1153	6.7	1152	4.8	1151	3.1	1143	35.4
	1174	29.4	1172	36.4			1154	6.0
C3–N4 + N2–Me stretch.	1184	5.7	1183	5.5	1176	71.0	1177	35.9
CH_3 rocking and CH_2 twisting	1255	34.7	1255	8.9	1255	40.4	1228	41.8
	1275	19.4	1275	60.7	1280	10.7	1281	39.0
N4–C5 + C3–N4 stretch.	1309	130.2	1306	232.9	1330	164.3	1330	210.4
CH_2 bending	1347	86.4	1349	64.3	1353	229.8	1365	82.3
N2–C3–N4 asym. stretch.	1400	214.3	1405	178.1	1381	151.0	1394	301.9
CH_3 def.	1438	9.0	1437	8.5	1437	10.1	1436	16.9
N–H bending	1442	11.4	1470	56.5	1517	181.9	1552	380.2
CH_3 def.	1470	14.5	1488	34.7	1470	8.4	1478	74.9
	1485	22.1	1499	57.3	1488	41.9	1492	38.5
	1503	3.9	1502	14.6	1502	3.7	1502	1.5
	1508	9.3	1506	17.1	1506	14.0	1504	14.0
	1512	9.1	1507	13.6	1511	24.4	1505	4.9
	1528	12.2	1530	155.6	1527	21.1	1515	80.2
N1–C7 stretch.	1716	27.6	1713	38.9	1718	11.9	1714	19.5
C3=O stretch.	1784	474.5			1784	506.8		
C5=O stretch.	1824	376.6	1824	430.0				
CH_3 and CH_2 stretch.	3040	2.1	3047	5.5	3028	2.2	3036	1.5
	3045	13.3	3049	6.8	3047	10.2	3049	8.4
	3070	37.6	3078	17.7	3071	37.4	3077	16.3
	3096	10.7	3100	8.8	3099	8.7	3102	7.2
	3155	14.9	3159	8.5	3158	12.9	3159	7.6
	3162	2.6	3165	3.0	3164	6.2	3166	5.3
	3163	8.2	3167	6.1	3176	1.6	3178	1.5
	3197	3.8	3192	4.7	3198	3.5	3193	4.4
N–H stretch.	3581	55.6	3574	55.9	3569	51.6	3562	47.4

Harmonic vibrational frequencies

The harmonic vibrational frequencies of the compounds under investigation have been summarized in Table 3. As it could be anticipated the force fields for the different tautomers are rather similar, but there are some differences that deserve to be commented. As indicated above, it can be observed that the C=O linkages present a stretching frequency that is characteristic of the relative position of the carbonyl group within the ring. In fact, our results indicate that this band appears at 1784 cm^{-1} for C3=O linkages, but it is blue-shifted by 40 cm^{-1} when the substituent is at position 5. The same happens with C=S stretching frequencies, although in this case it is not possible to assign a single absorption to this vibrational mode, because, as it is well known,[38] the C=S stretching mode appears usually coupled with other vibrational displacements.

Similarly, the C–Me stretching mode appears strongly coupled with the ring deformation modes. Consistent with the



Scheme 1

geometrical distortions discussed above, the C3 and C5 pyramidalization modes depend significantly on the nature of the substituent attached to the carbon atom. When this substituent is oxygen the former appear at frequencies higher than 700 cm^{-1}, while when the substituent is sulfur it appears shifted almost 100 cm^{-1} toward lower frequencies. Similar effects are observed for the latter. Also the N4–C5 stretch, which for the C5-oxo derivatives appears around 1305 cm^{-1}, is blue-shifted when oxygen is substituted by sulfur.

The N2–C3 and the C3–N4 stretching modes appear coupled in an out-of-phase combination around 1400 cm^{-1} for all the compounds investigated. The C3–N4 stretch appears also combined with the N4–C5 stretch and with the N2–Me stretch. The former corresponds to absorptions around 1300–1330 cm^{-1} and the latter to bands around 1180 cm^{-1}.

It is also interesting to note that the N–H stretching frequency shows a certain dependence on the nature of the substituents. For the dioxo derivative it appears at 3581 cm^{-1}, but it is red-shifted when one of the oxygen atoms is substituted by sulfur. Consistently, this red-shift is a maximum for the dithio derivative. It is also worth mentioning that similar red shifts were experimentally observed by Rostkowska *et al.*[28] when the IR spectrum of uracil was compared with those of the 2-thio, 4-thio and 2,4-dithio uracil derivatives. According to our results an even more pronounced sensitivity to the nature of the substituent should be observed as far as the N–H bending mode is concerned. In this case, the substitution of oxygen by sufur leads to a blue shifting, which is again maximum for the dithio derivative.

The N1–N2 stretching frequency changes with the nature of the substituent at C3. When the substituent is oxygen (**3O5O** and **3O5S**), the absorption band appears at 1010–1014 cm^{-1}. For the corresponding sulfur derivatives (**3S5O** and **3S5S**) it appears about 50 cm^{-1} red-shifted.

Unimolecular fragmentations of 1,2,4-triazepine radical cations

In order to gain some insight into the mechanisms associated with the unimolecular decompositions of 1,2,4-triazepines we have also studied the structure and bonding of the corresponding radical cations. The study of radical cations can present intrinsic problems, especially when high spin contamination affects the unrestricted calculation. In those cases where the spin contamination remains low, as in the molecules under study, the B3LYP formalism leads to geometries and energies in good agreement with high level *ab initio* calculations.[39,40] Our results (See Fig. 2 and Table 2) clearly show that the ionization of these compounds perturbs significantly the bonding characteristics of the seven-membered ring. On the other hand, these bonding perturbations depend significantly on the nature of the substituent at positions 3 and 5, and therefore are quite different when this substituent is an oxygen or a sulfur atom. When the substituent at positions 3 and 5 is an oxygen (**3O5O**), it can be observed, by looking at the changes in both the charge densities at the bond critical points (see Table 2) and the bond lengths, that linkages N2–C3, N4–C5, C5–C6 and, to a lesser extent, C7–N1 become significantly weaker. Concomitantly, the N1–N2, C3–N4 and to a lesser extent, C6–C7 become reinforced. These structural changes are consistent with the loss of –NHCO and $–CH_2CO$ observed experimentally[16] for this molecular ion.

When the substituent at position 3 is replaced by sulfur, the charge redistribution upon ionization is completely different than the previous case (see Table 2 and Fig. 2). The N2–C3 and the C3–N4 linkages now become reinforced, while the N4–C5 and the C6–C7 bonds become weaker. This changes are consistent with the loss of $–CH_2CO$ and seem to be at variance with the results of the mass spectrometry study,[16] which reports similar fragmentations to those observed for the oxygen analog. Nevertheless, a detailed analysis of the obtained intensities reflects a much more favorable loss of $–CH_2CO$ than –NHCO.

When the heteroatom at position 5 is a sulfur atom the only observed fragmentation is the loss of –NHCO for compound **3O5S** and –NHCS for compound **3S5S**. The conclusion of the experimental study is that in both cases the same bonds (N2–C3 and N4–C5) are broken. However, our theoretical calculations show significant differences in the bond activations of **3O5S** and **3S5S**. The geometries obtained in the present study show that in the **3O5S** molecular cation, the changes are more similar to those found for the **3O5O** derivative in the sense that N2–C3 becomes clearly weaker and to a lesser extent C5–C6, while the remaining bonds are unaffected or slightly reinforced (see Table 2). Hence, in this case one must conclude that the

only possible fragmentation would be that leading to the loss of –NHCO, in agreement with the experimental findings.[16] However, in the case of the **3S5S** radical cation the N2–C3 bond is reinforced instead of weakened and therefore we have to conclude that the observed loss of –NHCS does not come form the breaking of the N2–C3 and N4–C5 bonds, as proposed in the experimental study, but more likely from the breaking of the C3–N4 and C5–C6 bonds.

Prototropic tautomerism

Schematic representations of the corresponding PESs are given in Fig. 3. As indicated above, tautomer **I** is the most stable one in all cases, but there are significant differences regarding the relative stability of the remaining tautomers.

The first important differences affect the enolization mechanism of the oxo (or thione) groups attached to C5. This enolization can be produced either by a 1,3-H shift from the N–H group to yield species **IIb** or by a 1,3-H shift from the CH_2 group to yield structure **IVa**. Our results indicate that the first mechanism is thermodynamically favored when the heteroatom is sulfur, while the second is favored when the heteroatom is oxygen. Therefore, for **3O5S** and **3S5S** structure **IVa** is more stable than **IIb**, while the stability order is reversed for **3S5O** and **3O5O**. This difference can be understood by taking into account the relative strength of the bonds involved in the tautomerism. In compounds **3O5S** and **3S5S**, on going from the global minimum **I** to structure **IVa** one is replacing a C=S and a C–H bond by a C=C and an S–H bond, respectively, while for compounds **3S5O** and **3O5O** one replaces a C=O and a C–H bond by a C=C and an O–H linkage. Although an S–H bond is weaker than a C–H linkage, a C=C bond is significantly stronger than a C=S one, so that the overall prototropic process is more favorable for **3O5S** and **3S5S** than for compounds **3S5O** and **3O5O** where a C=O bond is replaced by a weaker C=C bond.

It should also be observed that even though tautomer **IVb** is more stable than **IIb** for compounds **3O5S** and **3S5S** by more than 3.0 kcal mol^{-1}, the corresponding energy barriers show that **IVb** is more difficult to obtain due to the high energy barriers involved (50.6 and 65.3 kcal mol^{-1} for **3O5S** and **3S5S**, respectively). This means that for these two compounds the most stable tautomer with respect to **I** is obtained through the highest energy barrier. For compounds **3S5O** and **3O5O** also the barriers to yield structure **IVa** are sizably higher than those leading to **IIb**.

The second important difference is that while for compound **3O5S** the **IIb** form is more stable than the **IIIa** one, for compound **3S5O** the stability order is reversed. This seems to indicate that the mercapto group is thermodynamically favored with respect to the hydroxy group, in agreement with the estimates of González *et al.*[41] who showed that, in general, for compounds presenting oxo and thione groups simultaneously, enethiol tautomers are more stable than the enol ones. Also importantly, the relative stability of the corresponding enethiol tautomers is independent of the nature of the second substituent. For example, for compounds **3S5O** and **3S5S** form **IIIa** is estimated to be 13.0 and 13.4 kcal mol^{-1}, respectively, above the global minimum. Similarly, for compounds **3O5S** and **3S5S** form **IIb** lies 11.9 and 11.7 kcal/mol^{-1}, respectively, above the global minimum.

For compounds **3S5S** and **3O5O**, where only a mercapto or a hydroxy group can be formed, tautomer **IIb** is slightly favored, although the tautomerization barriers are higher than those leading to tautomer **IIIa**. If one takes into account that this tautomerism can be viewed as the result of proton transfer from N4 towards the neighboring basic group, this seems to be consistent with our previous arguments, in the sense that the oxo (or the thione) group attached to C3 should be more basic than that attached to C5. It is worth noting, however, that even in those cases where structure **IIb** is predicted to be more stable that structure **IIIa**, the formation of structures **IIb** is kinetically less favorable than the formation of species **IIIa** since the activation barriers involved in the corresponding prototropic processes are systematically higher.

As a general rule the oxo-thiol forms of type **II** and **III** are destabilized with respect the oxo-thione ones by 12–13 kcal mol^{-1}. This energy gap is rather similar to that reported in the literature[21,23,24,29] for the thiouracil analogs. Also similarly to what was found for thiouracils, the mercapto group is less stabilized when it is attached to the carbon atom (C3) between the two nitrogen atoms of the ring. The enol-thione forms are 15–16 kcal mol^{-1} less stable than the oxo-thione ones. Once more, this energy gap is very close to that reported for thiouracils. In these cases, however, the structure where the enol group is attached to position 5 is slightly more stable than that in which it is attached to C3. Again, this behavior parallels that found for the thiouracil analogs.

Tautomer **V** implies a double hydrogen transfer: from NH to the heteroatom at position 3 and from the CH_2 group at position 6 to the heteroatom at position 5. This tautomeric form is always the least stable, and lies around 19–28 kcal mol^{-1} above the global minimum. Two different mechanisms can be envisaged to obtain this tautomer: a transfer from the NH group followed by a transfer from position 6 (**I** → **III** → **V**) or vice versa, that is a mechanism where the transfer from C6 is the first process (**I** → **IV** → **V**). According to our results the second path is always favored since the **III** → **V** hydrogen transfer implies the highest energy barrier in all the PES. This ratifies that, in general, the hydrogen shift from the CH_2 toward the neighboring heteroatom implies always activation barriers much higher than those required when the hydrogen transfer occurs from the NH group.

It is also worth noting that although for 2-, 4- and 2,4-thiouracils the oxo-thione and the dithione forms are also the most stable ones, the hydroxy-mercapto forms are rather stable, just next to the oxo-thione ones, in contrast with what is predicted for 1,2,4-triazepines. The enhanced stability of the hydroxy-mercapto forms of thiouracils was explained in terms of the tendency of the pyrimidine ring to adopt an aromatic structure. Obviously, this possibility is not open for seven-membered rings, explaining the low stability of these forms in the particular case of the triazepines.

In summary, in what concerns the tautomer stability, the most important conclusion is that for **3S5O** and **3O5S** the most stable tautomer is the oxo-thione form. Similarly, for **3S5S** and **3O5O** compounds the dithione and the dioxo forms, respectively, are the most stable ones. On the other hand, as shown in Fig. 3, the energy barriers connecting the different tautomers are very high, and therefore we can safely conclude that only the aforementioned tautomers will exist in the gas phase. In this respect, it should also be taken into consideration that the prototropic tautomerism processes investigated imply significant changes in the dipole moments, which may alter these relative stability patterns when examined in solution. The oxo- and thione forms already have quite large dipole moments, from 3.7 to 4.8 D (see Table 1), but their evolution towards structures **II** and **III**, which are the next most stable forms, is accompanied by a sizable increment of the dipole moment, which in some cases can be as large as 7.7 D. This implies that these forms should be preferentially stabilized in aqueous solution and very likely, independently of possible specific solvation effects associated with the formation of hydrogen bonds with the solvent, they should approach energetically the global minimum. In contrast, the formation of the less stable tautomers in the gas phase (forms **IV** and **V**) implies a sizable decrease of the dipole moment of the system (see Table 1) and therefore these tautomeric forms should not be favored in solution.

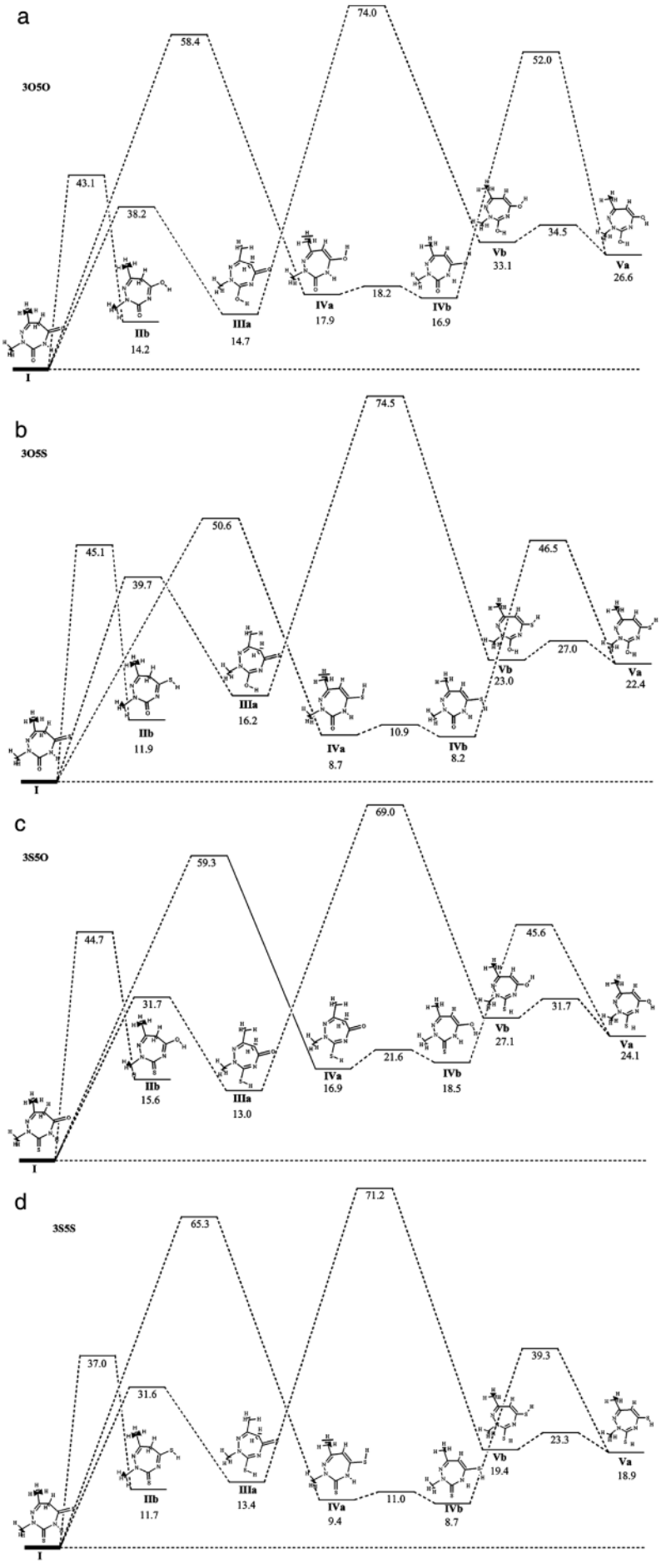


Fig. 3 Energy profiles corresponding to the unimolecular tautomerization processes. All values are in kcal mol^{-1}: (a) **3O5O**, (b) **3O5S**, (c) **3S5O**, (d) **3S5S**.

Conclusions

The relative stability of the oxo and thio derivatives of 1,2,4-triazepines are rather similar to those reported in the literature for uracil and its thio derivatives. The most stable tautomer corresponds systematically to the oxo-thione structure, followed by the corresponding oxo-mercapto or thione-mercapto forms. The oxo-hydroxy and the thione-hydroxy forms are slightly less stable, while the hydroxy-mercapto tautomers are the least stable ones. As for uracil and thio-uracil derivatives, the tautomerism activation barriers are high enough as to conclude that only the oxo-thione structures should be found in the gas phase. The relative stabilities should change, however, in aqueous solution because the corresponding prototropic tautomerisms are accompanied by significant changes in the dipole moment of the system.

The experimental conclusion[16] that ionization of 1,2,4-triazepines involved bonding changes that depend on the nature of the substituent at position 5 needs to be clarified: the fact that two unimolecular fragmentations are observed, leading either to a loss of –NHCX or $–CH_2CO$ when the substituent attached to C5 is oxygen, while when the substituent is sulfur only the former fragmentation is observed, does not imply that the bonds in the ring are similar dependent on the nature of the substituent at position 5. In fact, the calculated bond patterns in the corresponding radical cations are quite different, depending on the nature of the substituents at both positions 3 and 5. Then, although our results agree with the experimental data regarding the products of the unimolecular fragmentations, some of our proposed mechanisms are at variance with the ones suggested in ref. 16.

The bonding characteristics of the carbonyl and thiocarbonyl groups depend on their relative positions. When these groups are attached to C3, the C=O (or C=S) linkage is weaker than when it is attached to position 5. This is clearly reflected in the corresponding force field and should be easily detected in the corresponding infrared spectrum, as well as in the reactivitiy of these systems in the gas phase.

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