Substituent Effects on the Strength of the Intramolecular Hydrogen Bond of Thiomalonaldehyde

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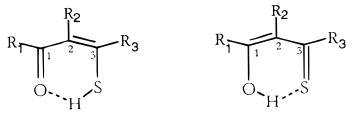
The effect of CH_3, NH_2, OH, and F substituents on the intramolecular hydrogen bond (IHB) of thiomalonaldehyde (TMA) was analyzed through the use of B3LYP density functional theory calculations. The geometries of the C1-, C2-, and C3-susbtituted enol and enethiol tautomers were optimized at the B3LYP/6-31G(d) level while their final energies were evaluated using a 6-311+G-(3df,2p) basis set expansion. In general C1-substitution strengthens the IHB of the enolic tautomer, while C3-substitution strengthens the IHB of the enethiolic form. These changes are related with an enhancement of the intrinsic acidity of the OH and the SH groups, respectively. Important cooperative effects are also present when the substituent can form an additional IHB with either the oxygen atom or the sulfur atom of TMA. However, the trends observed in the relative stabilities of the enol and the enethiol tautomers do not follow the changes observed in the strength of the IHB. C1-substitution specifically stabilizes the enethiol form, while C3-substitution stabilizes preferentially the enol tautomer. When substitution takes place at the central carbon atom, the enethiol tautomer is predicted to be slightly more stable than the enol counterpart. Substituent effects on the proton-transfer energy barrier are dramatic, and the interconversion between the enolic and the enethiolic forms of the C1- and the C3-substituted derivatives is barrier-free. In contrast, C2-substitution leads to an increase of the barrier.

Introduction

Among β-thioxoketones, thiomalonaldehyde (TMA) is one of the simplest compounds where an asymmetric prototropic tautomerism can be observed. The fact that these compounds exist as equilibrium mixtures of rapidly interconverting intramolecular hydrogen bonded *Z*-enol and *Z*-enethiol tautomeric forms has been well demonstrated on the basis of UV,[1] UV photoelectron,[2] IR,[1] and ^{1}H NMR[3,4] spectroscopic data. Actually, in the particular case of TMA, we have recently shown[5] that at the G2-(MP2) level of theory[6] both tautomers are nearly degenerate, with the *Z*-enethiol (**T**) 0.2 kcal/mol more stable than the *Z*-enol form (**E**) (see Scheme 1). In general, however, TMA tautomers containing S−H and C═O bonds are systematically 5−10 kcal/mol more stable than those with O−H and C═S bonds.[5] The enhanced stability of the cyclic enol tautomer **E** compared to the open chain structures is related to the existence of a stronger intramolecular hydrogen bond (IHB) and a significant resonance-assisted hydrogen bonding (RAHB)[7] with respect to the enethiol chelated tautomer, **T.**[5,8−10] This

Scheme 1



T **E**

RAHB effect, which strengthens the H-bond, is due to the 6 π electrons contained within the conjugated ring of these compounds, which make them potentially aromatic systems. Despite the RAHB effect, we also found that some open species of TMA, where no IHB is present, are very close in energy to **E** and **T**.[5]

As is well-known, the strength of a H-bond depends on the acidity of the proton donor and the basicity of the proton acceptor. Substituents can affect the strength of the IHB modifying the donor and acceptor abilities of the active centers of the molecule. The substituent may transmit its electronic effect to the reaction center by two principal mechanisms: the inductive effect and the resonance effect. The first one involves the interaction of substituent charges and dipoles with the reaction center, while the second is due to π-type interactions between the substituent and the reaction center. The second mechanism is predominant when both effects take place. Nevertheless, the idea of a well-defined substituent effect independent of the substrate to which it is attached is a simplifying assumption. The substituent effect in a particular substrate necessarily involves the mutual interaction of two groups. Substituent effects on the properties of many different compounds have been extensively studied[11] for many years. However, the effect of substituents on the strength of intramolecular hydrogen bonds has been much less investigated.[2,8,10]

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As far as substituted β-thioxoketones are concerned, we are only aware of the calculations of Millefiori and Di Bella.[10] They showed that substitution in the middle carbon of TMA does not change the geometry of the hydrogen bridge. The substitution effects at this position were previously found difficult to predict.[12] However, major perturbations of the IHB and of the RAHB should arise when the closest positions to the basic centers are substituted. This is of particular relevance for TMA, which stands as an appropriate model for investigating ultrafast laser pulse isomerization-controlled mechanisms.[13,14] In ref 15 it was concluded that suitable candidates for laser-driven hydrogen transfer (HT) should fulfill the requirements that the potential energy surface is asymmetric to distinguish between initial and final states and that there is a significant change in the dipole moment along the isomerization. Since these requirements may change upon substitution influencing the transfer rates, we have considered it of interest to analyze the electronic and steric consequences of substitution at the three possible positions of TMA (see Scheme 1). We will be concerned, in particular, with the relative stabilities of the enol and enethiol TMA derivatives in order to investigate whether the same degeneracy present in the parent compounds remains upon substitution. We shall also illustrate that substitution at C1 and C3 strongly affects not only the strength of the IHB but also the strength of other chemical bonds within the system as well as the proton-transfer barriers.

Computational Methodology

The ab initio calculations of the present study were performed using the Gaussian-94 series of programs.[16] The geometries of the different species under investigation were optimized at the B3LYP/6-31G(d) level which has been found[17] to give results in good agreement with high-level ab initio calculations as far as the description of intramolecular hydrogen bonds is concerned. The exchange functional B3[18] is a hybrid scheme proposed by Becke and composed of fractions of Hartree−Fock exchange and GGA exchange of Becke.[19] The hybrid functional so defined is used together with the correlation functional of Lee−Yang−Parr (LYP).[20] The corresponding harmonic vibrational frequencies were evaluated at the same level of theory by using second derivative techniques in order to confirm the nature of the critical points of the potential energy surface and to estimate the corresponding zero point energy (ZPE), which was scaled by the empirical factor 0.96 recently proposed by Curtiss et al.[21] Final energies were obtained in single-point calculations carried out at the B3LYP/6-311+G(3df,2p) level. This is the largest basis set expansion used in typical high-level ab initio formalisms as the G2 theory.[22]

The description of the charge redistribution which takes place upon substitution was done in terms of the atoms in molecules (AIM) theory of Bader.[23] For this purpose, the bond critical points (bcps) of the different species were located, i.e., points where the electron charge density hypersurface is minimum along the bond path connecting two nuclei of the system and maximum in the other two directions. The values of the charge density, $\rho(r)$, its Laplacian, $\nabla^2\rho(r)$, and the energy density, $H(r)$, at the bcps were useful in discussing the RAHB effects present in the chelated systems as well as in characterizing the IHB and its strength. At this point, it is important to remark that the charge densities at the bcps associated with inter- and intramolecular hydrogen bonds have been shown to bear a direct relationship to the strength of the linkage.[24] On the other hand, a comparison of the charge density of the parent compound with those of the corresponding substituted species allowed us to analyze the electronic redistributions associated with these processes. As shown by Bader et al.,[23] the Laplacian of the charge density indicates regions of space where the charge density is locally concentrated ($\nabla^2\rho(r) > 0$) or depleted ($\nabla^2\rho(r) < 0$). Likewise, negative values of $H(r)$ at the bcp imply stabilizing charge concentrations typically associated with covalent bonds. The topological analysis was carried out making use of the AIMPAC series of programs.[25] To complete the aforementioned study, the net atomic charges were calculated using natural bond orbital (NBO) analysis.[26]

Results and Discussion

The optimized geometries of the chelated ring substituted systems are given in Figure 1. The nomenclature used to designate the different species indicates the substituent (Me = CH_3, Am = NH_2, OH, F) and the position which has been substituted, according to the numbering shown in Scheme 1. **E** and **T** stand for enol and enethiol tautomers, respectively. Therefore, for instance, **E-Am1** designates the enolic form of the C1

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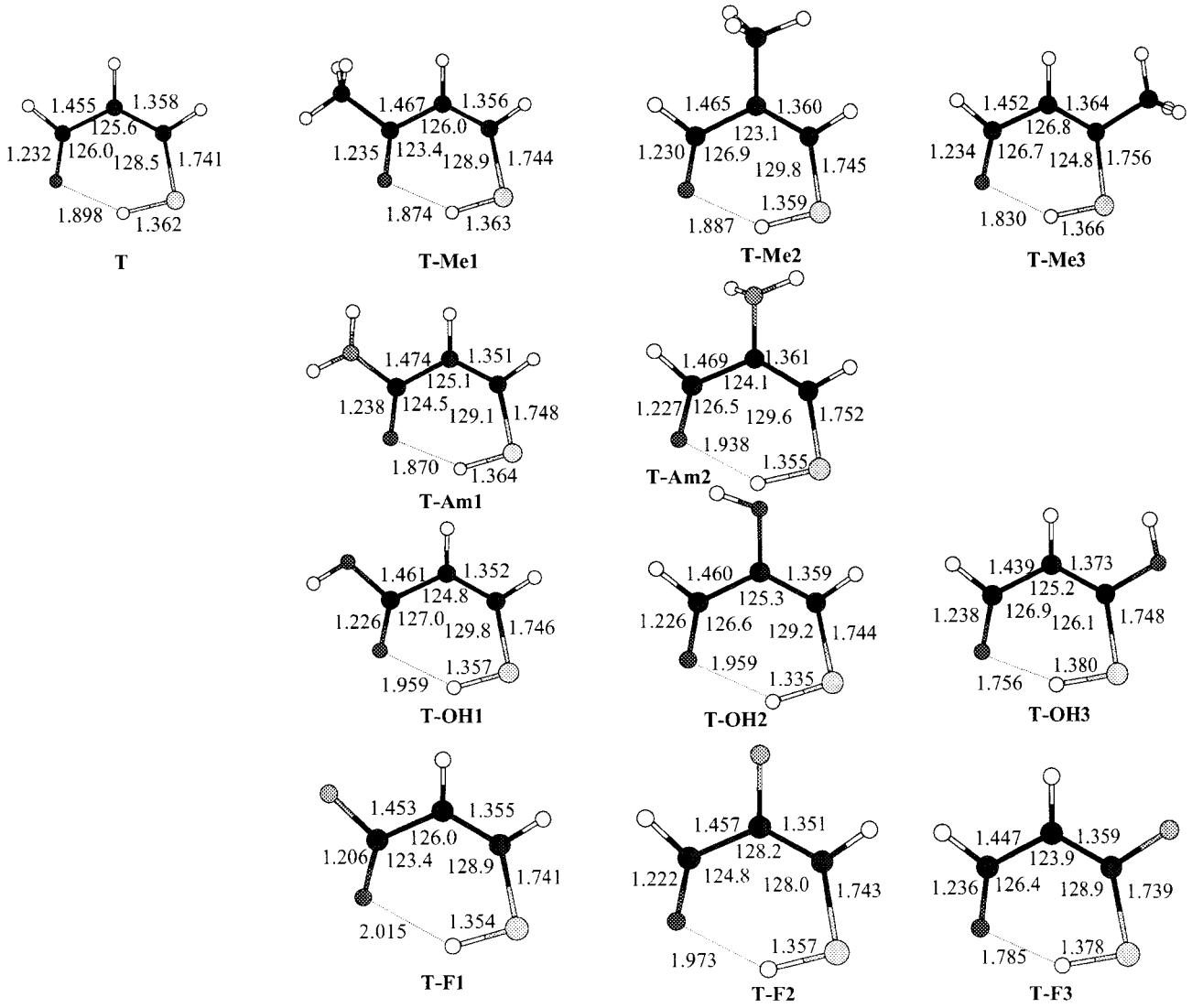


Figure 1. B3LYP/6-31G(d) optimized geometries for the different substituted thiomalonaldehyde derivatives. Bond distances in angstroms and bond angles in degrees.

amino substituted derivative. For the sake of an easier comparison, this figure includes also the geometries of the unsubstituted tautomers **E** and **T**, taken from ref 5. The four chosen substituents (F, OH, NH_2, and CH_3) model the different electronic mechanisms that can be envisaged between the substituent and the substrate.

Substituent Effects on Molecular Geometries. The magnitude of the substituent effects on the geometry varies significantly. Depending on the electronic donor or acceptor ability of the substituent, one should expect a fixed variation of the bond lengths with respect to the parent compound manifested in the lengthening of the single bond and the shortening of the double bond or vice versa and in concomitant changes of the bond angles. It can be observed, for instance, that methyl substitution systematically leads to a decrease of the internal angle centered at the substituted carbon, while the opposite is found upon fluorine substitution. In fact, the electron-withdrawing ability of the fluorine atom provokes an increase of the p character of the hybrid orbital that links the carbon to the fluorine. As a consequence, the other two bonds in which the substituted carbon participates increase their s character, leading to a larger bond angle. The methyl group, on the contrary, behaves essentially as an electron donor, and the effects are the opposite.

The changes affecting the bond lengths will be analyzed depending on the position substituted. In this respect, it is interesting to note that position C1 (or C3) of the enolic form is qualitatively equivalent to position C3 (or C1) of the enethiol tautomer, in the sense that in both cases the substituted carbon atom is engaged in a C═X (or C−XH) bond with the heteroatom (O and S, respectively). Indeed, the substituent effects observed in the enolic forms upon C1- (or C3)-substitution are qualitatively similar to those predicted for the C3- (or C1)-substituted enethiol, as we shall discuss later.

C1-methyl substitution increases the bond delocalization of the enolic form (**E-Me1**). The C1−C2 and C2−C3 bond lengths approach each other (see Figure 1) and the C═S bond lengthens. This effect is more pronounced when the substituent is an amino group because the inductive σ effect and the resonance π effect, associated with the conjugation of the nitrogen lone pair with the π-system of the parent compound, act in the same direction through a greater contribution of mesomeric forms b and c (see Scheme 2). In the case of the OH group, inductive and resonance mechanisms are combined too,

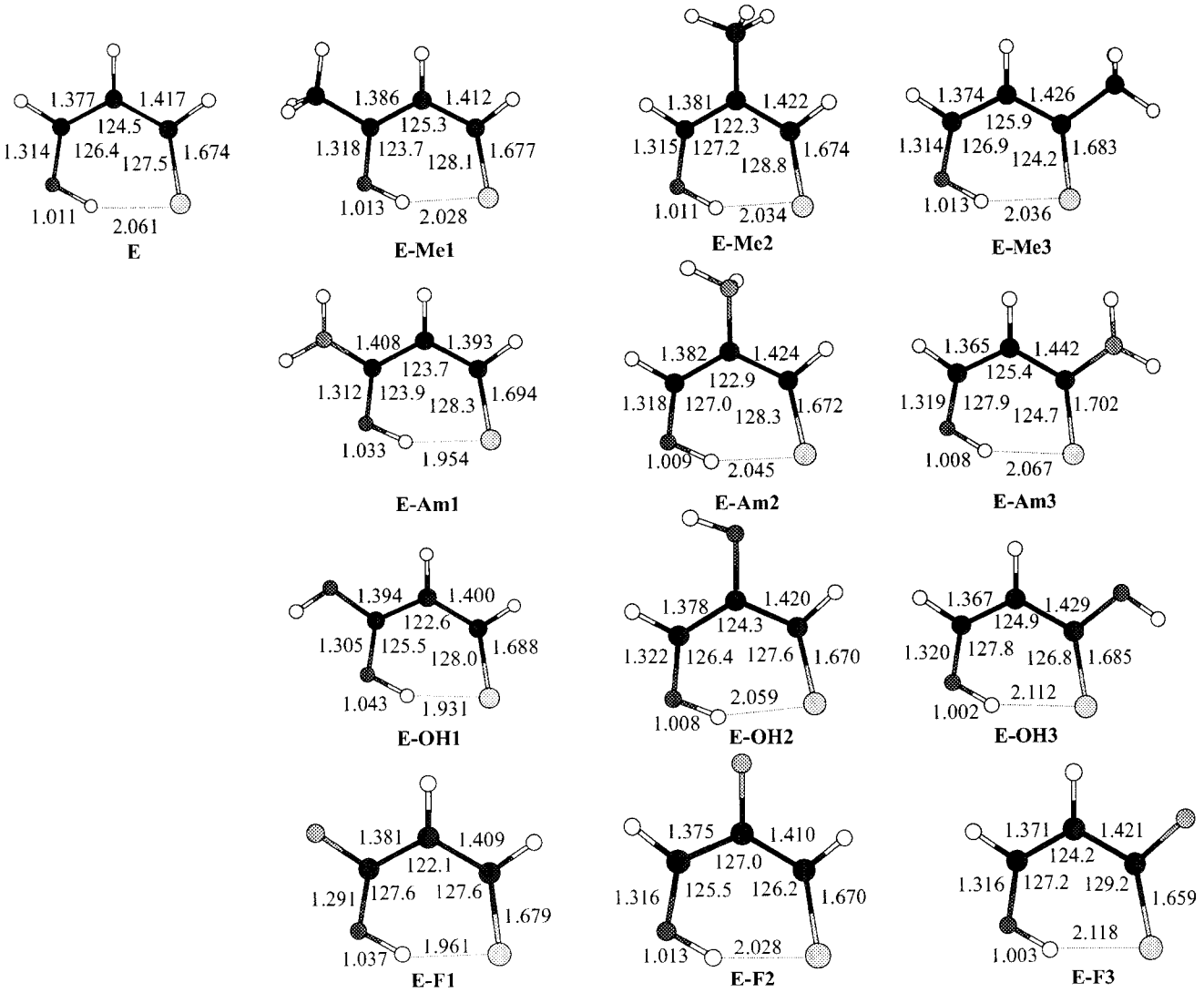
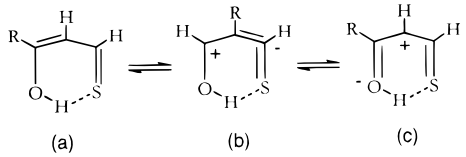


Figure 1. Continued.

Scheme 2



but the effects are smaller due to the higher electronegativity of the oxygen atom. The fluorine substitution effects are dominated by its σ-withdrawing ability, which leads to a significant shortening of the C−OH bond and to a slight lengthening (shortening) of the C1−C2 (C2−C3) linkage. It is also worth noting that in all cases the IHB becomes significantly shorter. As mentioned above, similar trends are observed when the enethiol tautomer is substituted at C3. In general, C3-substitution at the enethiol increases the bond delocalization and shortens the IHB.

C2-substitution effects, as pointed out previously by Millefiori et al.,[10] are not very dramatic, and the length of the IHB differs very little from that found in the unsubstituted enol form. Substituent effects are however more pronounced for the enethiol tautomer. In all cases, with excep for the methyl substituent, the IHB becomes longer, while the C═O bond shortens following the sequence Me < Am < OH < F. This indicates that as the electronegativity of the substituent increases, the substituted carbon atom becomes more and more electron deficient, withdrawing charge from its neighbors. This enhances the electronegativity of the carbonyl carbon, which polarizes the charge into the C═O bonding region, strengthening the linkage. Since sulfur is less electronegative and more polarizable than oxygen, similar effects, although smaller, should be expected for the C═S bond of the enol form.

C3-substitution effects on the enolic form, in contrast to those of C1-substitution effects, increase the bond localization and lengthen the IHB. As pointed out above, similar, although quantitatively different, effects are found for the enethiol form upon C1-substitution. For instance, if we concentrate our attention on the fluorine derivative, the shortening of the C═O bond (cf. Figure 1) in the enethiol tautomer is more than twice the shortening undergo by the C═S linkage in the enolic form, again due to the different nature of sulfur and oxygen.

It must be also noted that when the substituent is NH_2 or OH, an additional IHB between the substituent and one of the heteroatoms of the parent compound can be formed. For instance, in both **E-Am1** and **E-OH1**, one of

Table 1. Charge Density ρ and the Energy Density $H(r)$ at the Corresponding Bond Critical Points. All Values in a.u.

bond	ρ	$H(r)$	ρ	$H(r)$	ρ	$H(r)$	ρ	H(r)
	T		**T-F1**		**T-F2**		**T-F3**	
C═O	0.389	−0.650	0.419	−0.722	0.393	−0.658	0.386	−0.645
C−S	0.205	−0.170	0.205	−0.170	0.203	−0.168	0.208	−0.190
O···H	0.034	−0.155	0.026	0.000	0.029	0.000	0.043	−0.002
			T-OH1		**T-OH2**		**T-OH3**	
C═O			0.402	−0.680	0.393	−0.659	0.384	−0.642
C−S			0.203	−0.166	0.203	−0.166	0.205	−0.182
O···H			0.029	0.000	0.030	0.000	0.046	−0.002
			T-Am1		**T-Am2**		**T-Am3**	
C═O			0.391	−0.668	0.393	−0.657		
C−S			0.202	−0.164	0.200	−0.160		
O···H			0.036	−0.001	0.031	0.000		
			T-Me1		**T-Me2**		**T-Me3**	
C═O			0.388	−0.649	0.390	−0.650	0.386	−0.644
C−S			0.204	−0.167	0.203	−0.166	0.203	−0.164
O···H			0.036	−0.001	0.042	−0.006	0.040	−0.002
bond	ρ	$H(r)$	ρ	$H(r)$	ρ	$H(r)$	ρ	$H(r)$
	E		**E-F1**		**E-F2**		**E-F3**	
C−O	0.321	−0.509	0.350	−0.581	0.319	−0.506	0.319	−0.507
C═S	0.220	−0.266	0.218	−0.261	0.220	−0.265	0.222	−0.269
S···H	0.040	−0.005	0.050	−0.009	0.038	−0.005	0.036	−0.004
			E-OH1		**E-OH2**		**E-OH3**	
C−O			0.337	−0.554	0.316	−0.500	0.317	−0.503
C═S			0.215	−0.254	0.220	−0.266	0.215	−0.257
S···H			0.054	−0.010	0.040	−0.006	0.036	−0.004
			E-Am1		**E-Am2**		**E-Am3**	
C−O			0.331	−0.541	0.317	−0.503	0.398	0.505
C═S			0.213	−0.248	0.220	−0.266	0.208	0.242
S···H			0.051	−0.009	0.042	−0.006	0.040	−0.005
			E-Me1		**E-Me2**		**E-Me3**	
C−O			0.319	−0.508	0.319	−0.507	0.320	−0.510
C═S			0.219	−0.263	0.220	−0.266	0.218	−0.260
S···H			0.043	−0.007	0.042	−0.006	0.043	−0.006

the hydrogen atoms of the substituent is hydrogen bonded to the oxygen atom of the hydroxyl group, which behaves as a donor−acceptor. IHBs are also formed between the substituent and the sulfur atom of the thiocarbonyl group in species **E-Am3** and **E-OH3**, where the sulfur atom behaves as a double HB acceptor. A similar situation, but involving the oxygen atom of the carbonyl group, can be observed in species **T-Am1** and **T-OH1**. However, species **E-Am1** and **E-OH1** have no equivalent in the enethiol series. Any attempt to optimize the **T-Am3** form collapsed systematically to the corresponding enolic structure **E-Am3**, indicating that the sulfur atom of the thiocarbonyl group is not able to behave as HB donor−acceptor simultaneously. So, when the hydrogen atom of the NH_2 group in form **T-Am3** forms a HB with the sulfur atom, the proton of the S−H group migrates spontaneously toward the carbonyl oxygen, yielding the corresponding enol. Similarly, **T-OH3** is not a minimum of the potential energy surface, since the optimization of this structure also evolves, without activation barrier, to the **E-OH3** enolic species. However, an isomer with the OH group trans with respect to the thiocarbonyl group, avoiding the hydrogen bonding interaction with the sulfur, has been located.

In all the methyl derivatives, disregarding **T-Me3**, one of the hydrogens of the CH_3 group is in the plane eclipsing the double bond and favoring hyperconjugative effects. **E-Am3** and **T-Am1** species retain a C_s symmetry to favor the conjugation between the NH_2 lone pair and the C═S and C═O bonds, respectively, while in the 2-substituted derivatives this is not the case.

Substituent Effects in the Strength of the IHB. As indicated in the previous section, C1-substitution shortens significantly the IHB of the enolic form, reflecting a reinforcement of this linkage. This is also mirrored in an increase of the charge density at the corresponding bond critical point (See Table 1). This reinforcement of the IHB is essentially due to an increase of the donor ability of the OH group, which upon substitution becomes more acidic. This is confirmed when one compares the NBO net positive charge of the hydroxyl hydrogen in the fluorine derivative (+0.47) and that in the unsubstituted enolic form (+0.45). The effects of the substituent on the acceptor capacity of the C═S group must be negligibly small. According to these simple arguments, one should expect the IHB of the fluorine derivative **E-F1** to be the strongest of the whole series of C1-substituted enols. However, an inspection of the length of the IHB (see Figure 1) and the charge densities at the corresponding bcp (see Table 1) shows that this is not the case. Due to cooperative effects which are absent in **E-F1**, the OH derivative is the one which exhibits the strongest IHB. As mentioned above, in both the amino and the hydroxy derivatives there is also an IHB between the substituent and the oxygen of the OH group. This implies, following the arguments of Mó et al.,[24] that the OH group, which behaves as a base with respect to the substituent, should exhibit an enhanced acidity with respect to the C═S group, strengthening the IHB.

Consistently with our arguments of the previous section, C3-substitution in the enethiol form should increase the acidity of the SH group and the strength of the IHB. This is mirrored in the estimated bond lengths and bcp charge densities.

When the position substituted in the enol is C3, the situation is completely different and the IHB becomes longer (see Figure 1) and weaker as reflected by a smaller charge density at the bcp (see Table 1). This is due to a

Table 2. Total Energies (in hartrees), Unscaled ZPE Corrections (in kcal/mol), and Relative Energies Including Scaled ZPE Corrections for the Different TMA Derivatives. All the Relative Energies Refer to the Enethiolic Tautomer

	T-			TS-			E-		
	E_{total}	ZPE	ΔE	E_{total}	ZPE	ΔE	E_{total}	ZPE	ΔE
-F1	−689.51773	34.6	0.0	−689.50300	32.6	7.6	−689.50437	35.5	9.3
-F2	−689.48412	33.9	0.0	−689.47646	32.4	3.4	−689.48482	35.7	1.3
-F3	−689.49056	34.1	0.0	−689.48930	32.7	−0.5	−689.50290	36.3	−5.6
-OH1	−665.50179	42.7	0.0	−665.49069	40.9	5.3	−665.49239	43.3	6.6
-OH2	−665.46064	41.1	0.0	−665.45249	39.6	3.6	−665.46061	43.0	1.9
-OH3	−665.47428	41.9	0.0	−665.47292	40.5	−0.5	−665.49228	44.4	−8.9
-Am1	−645.62476	49.9	0.0	−645.61872	48.1	2.0	−645.62245	50.9	2.5
-Am2	−645.58876	49.5	0.0	−645.58057	47.8	3.5	−645.58873	51.3	1.8
-Am3							−645.62186	51.8	
-Me1	−629.55431	56.6	0.0	−629.54980	55.0	1.3	−629.55845	58.4	−0.8
-Me2	−629.54480	56.5	0.0	−629.53900	54.9	2.1	−629.54763	58.5	0.1
-Me3	−629.54974	56.6	0.0	−629.54568	55.1	1.1	−629.55380	58.4	−0.9

decrease of the intrinsic basicity of the carbonyl group, which becomes a poorer HB acceptor, while the effect on the intrinsic acidity of the OH group must be negligible. It is worth noting that in this case the amino- and the OH-substituted derivatives exhibit an anti-cooperative effect. Actually, in both **E-Am3** and **E-OH3** the sulfur atom behaves as a double HB acceptor, and therefore its basicity with respect to the OH group decreases.

Again, the same trends should be expected for the C1-substituted enethiol forms. In all cases, the methyl group constitutes an exception enhancing the intrinsic basicity of the thiocarbonyl (or the carbonyl) group of the enol (enethiol) tautomer, due to its electron-donor character.

When the position substituted is the central carbon atom (C2) of the enol tautomer, the effects of the substituent can be transmitted both to the OH group, whose acidity should increase slightly, and to the C═S group whose basicity should decrease slightly. Both effects are small and almost counterbalance each other. Hence, the IHB is only slightly perturbed. In the case of the enethiols, however, the decrease in the basicity of the C═O group dominates in relative terms with respect to the increase in the acidity of the SH group, and the IHB becomes, in general, weaker.

Substituent Effects on the Relative Sstability. One of the most important conclusions of our survey on the substituted derivatives of thiomalonaldehyde is that the relative stability of the enol and the enethiol forms does not follow the changes in the strength of the IHB discussed in the previous section. Taking into account that for the unsubstituted compound both **E** and **T** forms are practically degenerate, C1-substitution should stabilize more the enolic form, whose IHB significantly reinforces, and destabilize the enethiol tautomer whose IHB weakens. However, as shown in Table 2, **T-R1** (with the only exception being the methyl derivatives) are much more stable than the corresponding enolic forms **E-R1**. Similarly, on the basis exclusively of the changes in the strength of the IHB, one should conclude that for C3-substituted species the enethiol (**T-R3**) should be more stable than the enolic analogue (**E-R3**). Again, the relative stabilities appear reversed and the enolic form is systematically more stable than the enethiol tautomer. As shown in Table 2, the enethiol is also slightly more stable than the enol tautomer for the C2-substituted derivatives.

The obvious conclusion is that the substituent effects on the remaining chemical bonds of the system, in particular the C−O and the C−S linkages, clearly dominate. Actually we have already mentioned in preceding sections that when the substituent is attached to the carbonyl carbon (or to the thiocarbonyl carbon), the C═O (or the C═S) linkage reinforces significantly. Similarly, the strength of the C−OH (or C−SH) bond also increases when the substituent is directly attached to that carbon atom.

To gain some insight on the relative magnitude of these effects, we will use appropriate isodesmic reactions.

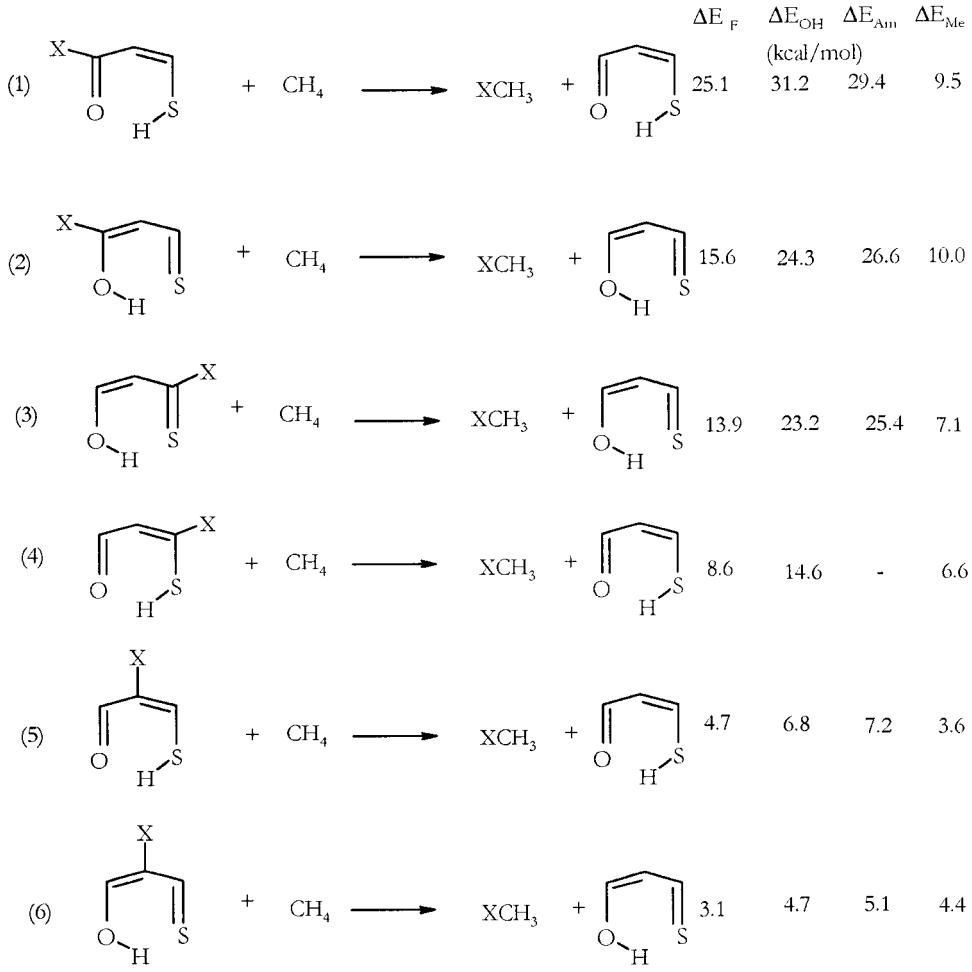
For the sake of conciseness in our discussion we will concentrate our attention initially on the subset of fluorine derivatives. Reactions 1 and 2 (Chart 1) permit us to compare the relative stability of the enol and the enethiol tautomers for C1-substittuted derivatives. A similar comparison for C3-substituted compounds can be attained through reactions 3 and 4. The first conspicuous fact is that both reactions 1 and 2 are endothermic, which indicates that both the enol and the enethiol tautomers are stabilized upon substitution. However, this stabilization is greater for the latter, indicating that the carbonyl function is more sensitive to substituent effects than the C−OH function. A similar qualitative conclusion can be attained in regard to the substituent effects on the stabilization of C═S and C−SH functions as shown by the endothermicity of reactions 3 and 4.

Hence, we may conclude that the enethiol tautomer is preferentially stabilized when the substituent enters position C1, while the corresponding enol form is preferentially stabilized when C3 is the substituted position.

The relative stabilities of the enethiol form as a function of the substituted position of reactions 1 and 4 can be compared. Reactions 2 and 3 give the same information for the enol tautomer. It can be seen that in both cases C1-substitution leads to a greater stabilization effect. Nevertheless the energy gap between C1- and C3-enethiol tautomers (16.5 kcal/mol) is much larger than that between the corresponding enol counterparts (1.7 kcal/mol), because oxygen-containing functions are more sensitive to substituent effects than the sulfur-containing analogues. Indeed, reactions 1 and 3 show that the C═S function is stabilized to a lesser degree than the C═O function. A similar finding was reported by Abboud et al.[27] for a wide set of carbonyl and thiocarbonyl derivatives. Consistently, the charge density at the C═O bcp

(27) (a) Abboud, J.-L.; Mó, O.; de Paz, J. L. G.; Yánez, M.; Esseffar, M.; Bouab, W.; El-Mouhtadi, M.; Moklisse R.; Ballesteros, E.; Herreros, M.; Homan, H.; López-Mardomingo, C.; Notario, R. *J. Am. Chem. Soc.* **1993**, *115*, 12648. (b) Molina, M. T.; Yánez, M.; Mó O.; Notario, R.; Abboud, J.-L. M. *The Chemistry of Double-bonded functional Groups, Supplement A3*; Patai, S., Ed.; John Wiley & Sons: New York, 1997; p 1355.

Chart 1



in **T-F1** is greater than that in the unsubstituted tautomer **T** and the energy density more negative, while the bond becomes 0.026 Å shorter. Similar but smaller effects are found for the C═S bond of **E-F3**. Analogously, reactions 2 and 4 are also endothermic, indicating that both the OH and the SH functions are stabilized by electronegative substituents. Again the OH function is more sensitive to substituent effects than the SH function and reaction 2 is 7.0 kcal/mol more endothermic than reaction 4. These differences are also reflected in the topology of the charge density of both tautomers. On going from **E** to **E-F1** the charge density at the C−OH bcp increases, the energy density becomes more negative, and the bond shortens. A comparison of the charge densities of **T** and **T-F3** shows that the substituent effects on the C−SH bond are similar but smaller.

Isodesmic reactions 5 and 6 compare the effect of C2-substitution on the relative stability of the enol and enethiol forms. As could be anticipated in light of our previous discussion, both reactions are only slightly endothermic. Reaction 5 is slightly more endothermic than reaction 6, because as mentioned before, when the substituted position corresponds to the central carbon atom the C═O function is more stabilized than the C═S one. This finding is also consistent with the topology of the charge distribution of both tautomers (See Table 1).

The endothermicity of reactions 1 and 2 for the other substituents, with the only exception being the methyl group, shows that the C1-substituted species are always more stable in the enethiolic form. Furthermore, a decreasing of these substituent effects following the sequence F > OH > NH_2 is observed because, as shown by the endothermicity of reactions 1 and 2, the C═O function is more stabilized than the C−OH function. However, the gap between both reaction energies decreases following the sequence F > OH > NH_2. This is due to a concomitant decrease of the electronegativity of the substituent and to the fact that the IHB between the substituent (OH or NH_2) and the oxygen atom of TMA must be stronger in the enolic form, where the oxygen atom of TMA behaves as a HB donor−aceptor, than in the enethiolic one, where the oxygen behaves as a HB bi-acceptor.

C3-substitutions favor the opposite effect: the **E** species are more stable than the **T** ones. The explanation is similar to the one offered above for the C1-substituted compounds, although in this case the thiocarbonyl group is the one which becomes preferentially stabilized. Since sulfur is less electronegative than oxygen, the observed effect is also smaller.

Substituent Effects on the Proton-Transfer Barriers. It is interesting to examine the effect of substitution on the tautomerization barriers. The energies for the transient species are given in Table 2. The inclusion of ZPE is crucial to correctly describe these barriers. As has been shown recently in the literature,[28] although in these systems there is a small energy barrier for the proton

(28) Garcia-Viloca, M.; Gelabert, R.; González-Lafont, A.; Moreno, M.; Lluch, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 10203.

transfer, the ground vibrational state is above the energy barrier. This happens for all C1- and C3-substituted derivatives when the substituent is NH_2, OH, or F. Therefore, these systems can be considered as good examples of low-barrier hydrogen bonds (LBHB),[29] which received a great deal of attention recently.[30] On the other hand, for NH_2, OH, and F substituents, a breaking of the degeneracy between the quasi isoenergetic **E** and **T** tautomers of TMA[5] takes place. Thus, it is reasonable to assume that for C1-substituted derivatives only the enolic form exists, whereas for the C3-substituted ones only the enethiolic tautomer should be present. For C2- substituted derivatives the transient species are higher in energy than both tautomers, and the estimated barriers (see Table 2) are about 2 kcal/mol larger than the ones found for the unsubstituted compound at the same level of theory.[5]

The methyl derivatives are an exception with respect to the aforementioned behavior, in the sense that, disregarding which is the substituted position, the proton transfer TS lies above both tautomers. As expected, the corresponding barriers do not change significantly with respect to that of the parent compound.

In summary, we conclude that the monosubstituted derivatives of TMA, with the only exception being the methylated species, do not fulfill the necessary conditions to induce a laser-driven hydrogen transfer.

Conclusions

We have shown that substituent effects on the IHB of thiomalonaldehyde are not negligible, mainly when the positions substituted are C1 and C3, while the effects are much smaller when the position substituted is the central carbon atom (C2). In general, C1-substitution implies a strengthening of the IHB of the enolic tautomer, while the IHB of the enethiolic form becomes stronger upon C3-substitution. These changes are related with an enhancement of the intrinsic acidity of the OH and the SH groups, respectively. Important cooperative effects are also present when the substituent can form an additional IHB with either the oxygen atom or the sulfur atom of thiomalonaldehyde. The RAHB effect is reinforced upon C1-substitution which enhances bond delocalization, while the opposite effect is observed when the position substituted is C3.

Quite importantly, although the enolic and the enethiolic forms of the unsubstituted compound are nearly degenerate, they are not when any of the three positions of the system undergoes substitution. C1-substitution specifically stabilizes the enethiol form, which becomes the most stable one, while upon C3-substitution the enol becomes the most stable tautomer. When substitution takes place at the central carbon atom (C2), the enethiol tautomer is predicted to be slightly more stable than the enol counterpart. Methyl substituent constitutes an exception to these rules, and upon methyl substitution the enethiol form is slightly more stable than the enol one.

Also importantly, the trends observed in the relative stabilities of the enol and the enethiol tautomers do not follow the changes observed in the strength of the IHB. In general, they show the different sensitivity of the C═O and C═S linkages to substituent effects. As already shown in the literature,[27] substituent effects are more pronounced in carbonyl than in thiocarbonyl functions. A similar behavior is observed in regard to the relative stability of C−OH and C−SH linkages.

Substituent effects on the proton-transfer energy barriers are dramatic. While the enol and the enethiol forms of the unsubstituted compound are separated by an energy barrier of ca. 2 kcal/mol,[5] the interconversion between the enolic and the enethiolic forms of the C1- and the C3-substituted derivatives is barrier-free. Accordingly, C1-substituted derivatives should exist only in the enethiolic form, while C3-substitttuted compounds should exist exclusively as enolic tautomers. Only when the substituent is attached to the central atom does the proton-transfer barrier increase, and therefore both tautomers should be present in the gas phase.

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(30) See for instance: Cleland, W. W.; Kreevoy, M. M. *Science* **1995**, *269*, 104. Cassidy, C. S.; Lin, J.; Frey, P. A. *Biochemistry* **1997**, *36*, 4576. Kahyaoglu, A.; Haghjoo, K.; Guo, F.; Jordan, F.; Kettner, C.; Felföldi, F.; Polgár, L. *J. Biol. Chem.* **1997**, *272*, 25547.