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Thioenols and thioamides substituted by two β-EWGs. Comparison with analogous amides and enols

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Condensation of organic isothiocyanates with active methylene compounds gave nine thioamides RNHCSCHYY′ or their isomeric thioenols RNHC(SH) = CYY′ for substrates in which Y and Y′ are electron-withdrawing groups (EWG). These included derivatives of Meldrum's acid (MA) which showed 100% thioenol in all solvents. For other compounds the percentages of thioenol in $CDCl_3$ when R = Ph are 100% when Y = CN and Y′ = CO_2Me or Y′ = $CO_2CH_2CCl_3$, 6% when Y = Y′ = $CO_2CH_2CF_3$, and 0% when Y = Y′ = CO_2Me. The chemical shift of SH (highest values 12.0–16.0 ppm) served as a probe for the thioenol structures and also for the extent of hydrogen bonding to the SH group. In contrast to simple ketones and thioketones in which thioenolization is favored over enolization by factors as large as 10^6, for intramolecular competition $K_{Thioenol}/K_{Enol}$ ratios are much lower than for systems not substituted by β-EWGs. X-ray crystallography of the 5-anilido-MA derivative shows a hydrogen-bonded thioenol structure. δ(OH), δ(NH), K_{Enol}, and crystallographic data for analogous thioenol and enol systems are compared.

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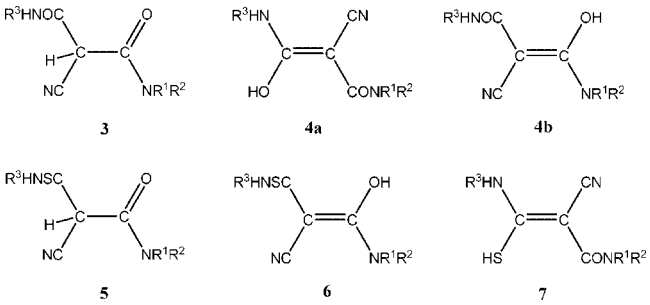
Keywords: enolization; thioenolization

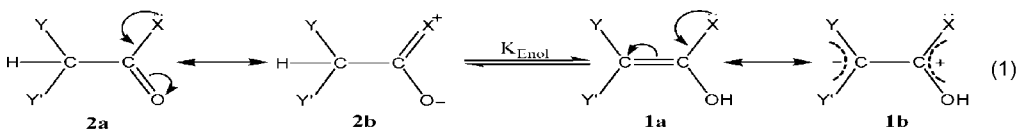
INTRODUCTION

Enols of carboxylic acid amides (**1**) are relatively unstable compared with the amides (**2**).

In the last decade we have succeeded in stabilizing these enols and other enols of carboxylic acid derivatives by substituting the C_β carbon atoms with electron-withdrawing groups (EWGs) Y and Y′ capable of delocalizing negative charge by resonance.[1–13] This is due to the higher stabilization of the delocalized zwitterionic contributing structure **1b** of the enol than of the amide contributing structure **2b** by Y,Y′ (Eqn (1)). The latter is usually regarded as the reason for the low extent of enolization of the amides. As a part of our studies of enolization of carboxylic acid amides we recently studied the enolization of cyano malonamides **3**[12] to their enols **4a** or **4b** and compared the extent of enolization in terms of the equilibrium constant



(a) of K_{Enol} for **3** with K_{Enol} for **5**, which compares the influence of a nonenolizing C=O *versus* C=S on the extent of enolization of two different analogous systems, and (b) of K_{Enol} for **5** *versus* $K_{Thioenol}$ for **5** which compares competing enolization and thioenolization.



X= OH, OR, NRR', OCOR, Halogen

K_{Enol} = [enol]/[amide] to that of cyano monothiocarbonylmalonamides **5**.[13] For the compounds with structure **5** both enolization to the enol–thioamides **6** with K_{Enol} = [**6**]/[Amide–thioamide], and thioenolization to the amide–thioenols **7** tautomers with $K_{Thioenol}$ = [**7**]/[**5**] were observed. Two comparisons were made:

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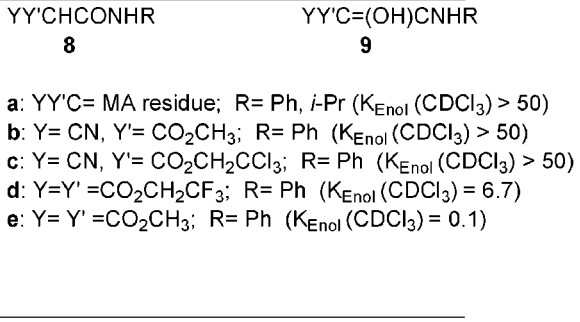
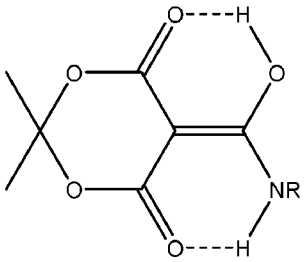
The observed results are that K_{Enol}(**3**) > K_{Enol}(**5**), so that the combination of Y,Y′ = CN, CSNRR′ is less efficient in promoting enolization than CN, CONRR′.[12,13] Comparison of K_{Enol}(**5**) with $K_{Thioenol}$(**5**) shows that K_{Enol} is mostly higher, although when R is an aromatic group, the extent of enolization and thioenolization is approximately similar, and the latter is sometimes even slightly higher.[13]

This is not the case for enols and thioenols which are not activated by β-EWGs. On comparing such 'simple' systems (i.e., substituted only by alkyl or aryl groups) the thioenolization is more extensive by several orders of magnitude.[14–20] This is also the case for enols of carboxylic acid esters and thioesters,[21,22] as discussed below.

In the present paper we compare a few examples of the previously investigated amides **8**/enols **9** activated by β-EWGs and the corresponding thioamides **10**/thioenols **11**. Systems **8**/**9** include 'formal' ('formal' is used to emphasize that the amides appear frequently in mixtures with their enols or thioenol tautomers) amides substituted by Meldrum's acid (MA) moiety (e.g., **8a**,[1] for which the structure of the enol **9a** is shown) or by combination of a CN group with an ester group such as CO_2CH_3 (**8b**)[2] or $CO_2CH_2CCl_3$ (**8d**)[9] or a combination of two ester groups, for example, $CO_2CH(CF_3)_2$ and $CO_2CH_2CF_3$.[6] Two $CO_2CH_2CF_3$ groups (**8d**/**9d**) generate a relatively stable enol (K_{Enol} = 6.7),[6] whereas two CO_2Me groups (**8e**/**9e**) give a low K_{Enol} of 0.1.[1] For the thioamides **10**/thioenols **11** we determined the percentage of thioenol as a function of the solvent, the thioenols' NMR chemical shifts and their structures.

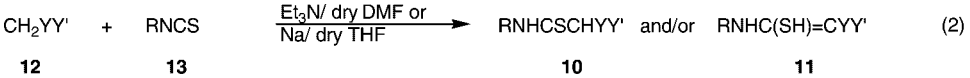


gave nine thioamides (**10a-i**)/ thioenols (**11a-i**) or their mixture (Eqn (2)), depending on Y, Y′, R, and the solvent. Compounds **11a**,[23] **11d**[24], and **11i**[25] are known.



9a

The MA derivatives **11a–c** were prepared with the expectation that similarly to the MA activated enols of amides, the enolization will not take place on the ester carbonyls,[1,7] but on the 5-C=S group. Indeed, as shown in Fig. 1 this the case and **11a** is the first example of an X-ray structure of a noncyclic thioenol of a thioamide activated by two β-EWGs. **11a** is also exclusively the thioenol in all solvents (as shown below). The solid state parameters of **11a** are compared with those of the analogous enol **9a**, R = Ph[1] in Table 1. The C—S single bond length is 1.739(2) Å, compared with 1.693 Å for a double C=S bond of thioamides,[26] and the 'enolic' double bond of 1.425(3) Å, is only slightly shorter than the other C_α—C_β bonds. The C=O bond lengths are longer than those in normal esters and the slightly longer bond (1.229(3) Å) of the C=O *cis* to the SH indicates a stronger C=S···H—O hydrogen bond than of the C=O···H—N bond (with C=O bond length of 1.220(3) Å). The S1—H bond length and the hydrogen bonded O2···H distance are 1.22(4) Å and 1.76(4) Å, respectively, with S1···O2 non-bonding distance of 2.9026(18) Å and SHO angle of 152(3)°. Another intramolecular hydrogen bond is N1—H···O1 with N—H, O···H, and N···O length and distances of 0.84(3), 1.90(3), and 2.604(2) Å, respectively. The doubly hydrogen bonded system with S1—H···O2 and N1—H···O1 moieties can thus serve as a model for an activated thioenol. For other data refer to Supplementary data.



12a: YY'C= MA residue
12b: Y= CN, Y'= CO_2CH_3
12c: Y= CN, Y'= $CO_2CH_2CCl_3$
12d: Y=Y' =$CO_2CH_2CF_3$
12e: Y= Y' =CO_2CH_3

13a: R= Ph
13b: R= 1-Np
13c: R= *i*-Pr

10a/11a: YY'C= MA residue; R = Ph
10b/11b: YY'C= MA residue; R = 1-Np
10c/11c: YY'C= MA residue; R = *i*-Pr
10d/11d: Y= CN, Y'= CO_2CH_3; R= Ph
10e/11e: Y= CN, Y'= CO_2CH_3; R = 1-Np
10f/11f: Y= CN, Y'= $CO_2CH_2CCl_3$; R = Ph
10g/11g: Y=Y' =$CO_2CH_2CF_3$; R = Ph
10h/11h: Y=Y' =$CO_2CH_2CF_3$; R = 1-Np
10i/11i: Y= Y' =CO_2CH_3; R = Ph

RESULTS

Reactions of five active methylene compounds CH_2YY' **12** where Y,Y′ are two ester groups or a cyano and an ester group, with organic isothiocyanates (**13**) in the presence of dry Et_3N or Na

Structure in solution: NMR spectra, configuration, and $K_{Thioenol}$ values

Dissolution of substrates **10/11** in different solvents establishes immediately an equilibrium between the amide and thioenol species, which did not change with time, that is, the equilibration

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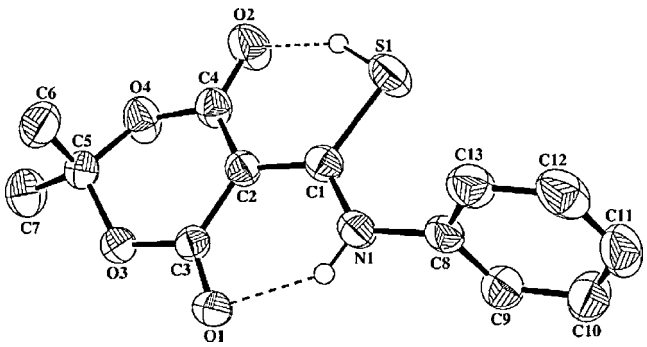


Figure 1. ORTEP drawing of **11a**

is instantaneous under our conditions. The ^{1}H and ^{13}C NMR spectra were recorded for all systems investigated. Selected ^{1}H and ^{13}C NMR spectral parameters are given in Table 2. The complete NMR data are given in Tables S1 and S2 of the Supplementary data. The SH chemical shifts (in $CDCl_3$ or CCl_4) are at a lower field than in many aliphatic and alicyclic thioenols (2.13–2.85 ppm),[27–31] in $Ph_2C{=}C(SH)Ph$ (3.28 ppm),[15] or in polyfluorinated thioenols (3.6–4.1 ppm).[31] In our systems the δ(SH) values for the MA derivatives **11a–c** are the highest at 12.02–16.04 ppm (12.02–14.17 ppm in $CDCl_3$; $\delta = 9.81$ for **11b** in DMSO-d_6 is an exception). These values are ascribed to strong S—H···O=C hydrogen bonds. Only for the cyano ester **11d–f** configurational isomers are possible since in **11g–i** the two β-ester groups are identical and there are both S—H···O and N—H···O hydrogen bonds to their *cis*-CO_2R groups (Scheme 1). The hexafluoromalonic ester derivatives **11g** and **11h** in which the hydrogen bonds are weaker display moderate δ(SH) values at 4.95–7.40 ppm. Since the geometry does not allow intramolecular CN···H—S hydrogen bonds, the δ(SH) values are lower (4.61–4.83 ppm) in the cyanoesters **11d–f**. The N—H···O hydrogen bonds are stronger than S—H···O bonds, and in **11d–f** the former is the only hydrogen bond formed. The δ(SH) have the lowest values of 4.61–4.83 ppm and the structure is that of the *E*-thioenol (Scheme 1), with the SH group weakly associated with the solvent. The higher values in DMSO-d_6 are due not to the δ(SH), but to the proton formed on ionization of the thioenol, as found for enols in this high dielectric constant solvent.[5] The NH signals for all the enols appear at 11.26–12.97 ppm, with the highest values for the MA derivatives. Their small range is consistent with the presence of N—H···O hydrogen bonds in all of them and an *E*-configuration in **11d–f**.

Indeed, in β-thioxoesters $HSC(R^1){=}CHCO_2R^2$ the intramolecular S—H···O= hydrogen-bonded *Z*-isomer displays δ(SH) at 5.68–8.19 ppm, whereas for the *E*-isomer the δ(SH) is at *ca.* δ 3.80 ppm.[32]

Table 3 displays the product distributions for all the **10**/**11** isomers in several solvents and the derived $K_{Thioenol}$ values. For comparison, the previously obtained K_{Enol} values of the analogous **8**/**9** isomers[1,2,6,7] are given. For 'formal' thioamide systems **10a–i**, complete thioenolization was obtained for the MA and the cyanoester derivatives **11a–f** were obtained, similarly to the analogous enol derivatives **8/9a,b**.[1,2] For the trifluoroethylmalonic esters, the percentages of thioenol in $CDCl_3$ are 13% for **11h** and 6% for **11g**, compared with 87% for the analogous enol **9d**.[6] No thioenolization was obtained for the dimethyl malonate system **11i** in $CDCl_3$, whereas the analogous amide enolized in 5–10%.[1] Consequently, enolization is more extensive than thioenolization for these systems.

There are limited data for the solvent effect on the thioenolization (Table 3), since the reaction is complete for several systems in all solvents. Where data are available $K_{Thioenol}$ decreases in the order $CDCl_3 > CD_3CN >$ DMSO-d_6 as found earlier for enol systems[1–3,6–9,11–13] and this is attributed to the higher polarity of the amide than of the hydrogen bonded enol.

DISCUSSION

Enolization on C=O versus thioenolization on C=S

The relative ease of enolization *versus* thioenolization was previously compared. Qualitatively, on comparing structurally

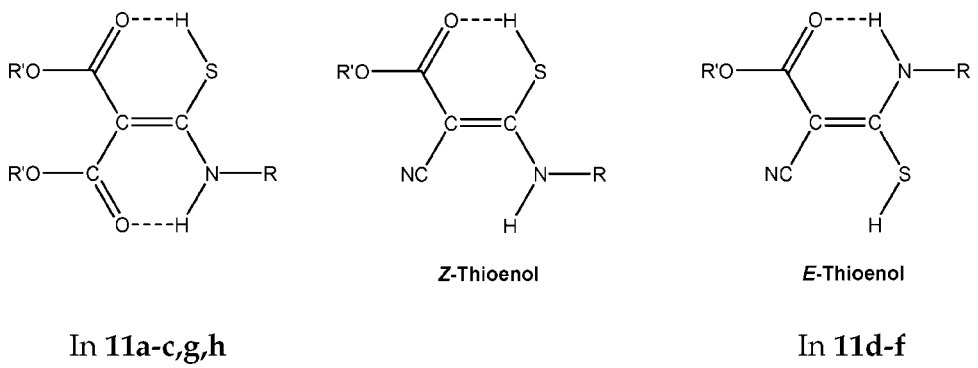
Table 1. Comparison of selected X-ray data for Meldrum's acid derivatives **9a** (R = Ph)[1] and **11a** (R = Ph) at room temperature

	Lengths (Å)			Degree (°)	
Bond	**11a**	**9a**	Angle	**11a**	**9a**
C(1)–C(2)	1.425 (3)	1.426 (5)	S(1)–C(1)–N(1)	115.27 (17)	—
C(1)–N(1)	1.324 (3)	1.333 (4)	O(1)–C(1)–N(1)	—	118.4 (4)
C(1)–S(1)	1.739 (2)	—	S(1)–C(1)–C(2)	123.85 (16)	—
C(1)–O(1)	—	1.300 (4)	O(1)–C(1)–C(2)	—	120.1 (3)
C(2)–C(3)	1.445 (3)	1.414 (5)	N(1)–C(1)–C(2)	120.88 (19)	121.5 (3)
C(2)–C(4)	1.436 (3)	1.420 (5)	C(1)–C(2)–C(3)	118.74 (18)	122.4 (3)
C(3)–O(1)	1.220 (3)	1.221 (4)	C(1)–C(2)–C(4)	122.60 (19)	117.2 (3)
C(4)–O(2)	1.229(3)	1.240 (4)	C(2)–C(3)–O(1)	126.52 (19)	126.1 (3)
S(1)–H(S1)	1.22 (4)	—	C(2)–C(4)–O(2)	127.1 (2)	116.9 (3)
O(1)–H(O1)	—	1.125	C(1)–N(1)–C(8)	125.44 (19)	130.3 (3)
N(1)–H(N1)	0.84 (3)	0.942	S(1)–H···O(2)	152 (3)	—
O(2)···H(S1)	1.76 (4)	—	O(1)–H···O(2)	—	158.24
O(2)···H(O1)	—	1.385	N(1)–H···O(1)	141 (3)	138.54
O(1)···H(N1)	1.90 (3)	1.939	—	—	—

Table 2. Selected ^{1}H (CH, SH, NH) and ^{13}C (CH, C_{β}, C═S, C_{α}) chemical shifts for systems **10**/**11** in several solvents at room temperature

Compd.	R	Solvent	Species	CH	SH	NH	CH or C_{β}	C═S or C_{α}
10a/11a	Ph	$CDCl_3$	Thioenol	—	12.02	12.93	83.11	178.71
		THF-d_8	Thioenol	—	13.72	12.97	83.26	179.98
		CD_3CN	Thioenol	—	12.79	12.25	83.48	179.23
		DMSO-d_6	Thioenol	—	12.67	11.52	84.11	179.59
10b/11b	1-Np	$CDCl_3$	Thioenol	—	13.16	11.44	83.44	179.79
		THF-d_8	Thioenol	—	13.17	13.09	83.50	180.99
		CD_3CN	Thioenol	—	12.97	11.72	83.90	179.81
		DMSO-d_6	Thioenol	—	9.81	12.86	84.53	181.41
10c/11c	*i*-Pr	$CDCl_3$	Thioenol	—	14.17	11.33	81.85	177.99
		THF-d_8	Thioenol	—	16.04	11.31	82.29	180.63
		CD_3CN	Thioenol	—	14.32	11.26	82.07	178.50
		DMSO-d_6	Thioenol	—	12.43	11.31	82.40	178.56
10d/11d	Ph	$CDCl_3$[b]	Thioenol	—	4.71	11.68	72.55	169.40
10e/11e	1-Np	$CDCl_3$	Thioenol	—	4.61	11.91	72.62	170.72
		CD_3CN	Thioenol	—	4.69	11.73	72.38	169.62
		DMSO-d_6[c]	Thioenol	—	8.76	12.26	76.20	179.83
10f/11f	Ph	$CDCl_3$	Thioenol	—	4.83	11.48	71.88	171.04
		DMSO-d_6[c]	Thioenol	—	11.19	11.83	72.32	Not observed
10g/11g	Ph	$CDCl_3$	Thioamide	5.31	—	10.33	65.89 (d, J = 141.8 Hz)	185.01 (d, J = 5.7 Hz)
			Thioenol	—	4.95	11.95	a	a
		CD_3CN	Thioamide	5.25	—	10.26	65.63 (d, J = 134.2 Hz)	188.75 (d, J = 6.5 Hz)
10h/11h	1-Np	$CDCl_3$	Thioamide	5.49	—	10.53	65.36 (d, J = 141.2 Hz)	187.69 (d, J = 5.8 Hz)
			Thioenol	—	6.75	12.24	87.56	174.01
		THF-d_8	Thioamide	5.54	—	11.12	65.57 (d, J = 135.4 Hz)	190.41 (d, J = 6.7 Hz)
			Thioenol	—	7.40	11.59	a	a
		CD_3CN	Thioamide	5.50	—	10.47	65.04 (d, J = 135.2 Hz)	191.61 (d, J = 6.9 Hz)
		DMSO-d_6	Thioamide	5.68	—	12.24	64.63 (d, J = 131.5 Hz)	191.72 (d, J = 7.1 Hz)
10i/11i	Ph	$CDCl_3$	Thioamide	5.05	—	10.68	66.74 (d, J = 142 Hz)	186.80 (d, J = 5.5 Hz)
		DMSO-d_6	Thioamide	5.15	—	11.90	66.53 (d, J = 143.8 Hz)	190.32 (d, J = 6.8 Hz)

[a] The percentage of thioenol is low, not enabling to record its ^{13}C signals.
[b] The compound ionizes to the thioenolate ion in both CD_3CN and DMSO-d_6.
[c] Ionizes in DMSO-d_6.



Scheme 1. Configurations of and hydrogen bonding in compounds **11**

analogous systems with one enolization site R′RCH—C═X (X═O, S), thioenolization is much more facile than enolization. Simple thioenols are observable species[14] whereas the corresponding enols are less stable than their carbonyl tautomers.[33] Only recently a few quantitative data were obtained for such competition. The triarylethenethiols, **14**, X═S, Ar = Ph, *p*-An do not isomerize to the thioketones at 60 °C in hexane after 2 weeks and $K_{Thioenol}$ of ≥ 100 in hexane was estimated.[15] In

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Table 3. Effect of Y, Y′, R and the solvent on $K_{Thioenol}$ for **10/11** systems, compared with K_{Enol} for the **8/9** systems

Compd.	R	Solvent	(%) TA[a]	(%) TE[b]	$K_{Thioenol}$	Compd.	(%) Enol[c]	K_{Enol}
10a/11a	Ph	$CDCl_3$	0	100	≥50	**8a/9a**	100	≥50
		THF-d_8	0	100	≥50		—	≥50
		CD_3CN	0	100	≥50		100	≥50
		DMSO-d_6	0	100	≥50		100	≥50
10b/11b	1-Np	$CDCl_3$	0	100	≥50		—	—
		THF-d_8	0	100	≥50		—	—
		CD_3CN	0	100	≥50		—	—
		DMSO-d_6	0	100	≥50		—	—
10c/11c	*i*-Pr	$CDCl_3$	0	100	≥50	**8c/9c**	100	≥50
		THF-d_8	0	100	≥50		100	≥50
		CD_3CN	0	100	≥50		100	≥50
		DMSO-d_6	0	100	≥50		0	≤0.02[b]
10d/11d	Ph	$CDCl_3$	0	100	≥50	**8d/9d**	100	≥50
		DMSO-d_6	0	100	≥50		0	≤0.02
10e/11e	1-Np	$CDCl_3$	0	100	≥50		—	—
		DMSO-d_6	0	100	≥50		—	—
10f/11f	Ph	$CDCl_3$	0	100	≥50	**8f/9f**	100	≥50
		CD_3CN	85	15	0.18		50	1
		DMSO-d_6	0	100	≥50		0	≤0.02[b]
10g/11g	Ph	$CDCl_3$	94	6	0.07	**8g/9g**	87	6.7
		CD_3CN	100	0	≤0.02		5	0.05
		DMSO-d_6	100	0	≤0.02		0	≤0.02
10h/11h	1-Np	$CDCl_3$	87	13	0.15		—	—
		THF-d_8	100	0	≤0.02		—	—
		CD_3CN	100	0	≤0.02		—	—
		DMSO-d_6	100	0	≤0.02		—	—
10i/11i	Ph	$CDCl_3$	100	0	≤0.02	**8i/9i**	<10	≤0.1
		DMSO-d_6	100	0	≤0.02		0	≤0.02

[a] Thioamide.
[b] Thioenol.
[c] From previous work on systems **8/9**.
[d] The anion was obtained.

contrast, K_{Enol} for $Ph_2C{=}C(Ph)OH$ at 295 K is *ca.* 0.06 in DMSO, the best enol stabilizing solvent.[16] It is estimated that $K_{Thioenol}/K_{Enol}$ for **14**, Ar = Ph is $\geq 10^6$.[16] A similar ratio was extrapolated for the $PhC(R){=}C(XH)CH_2Ph$, X = S, O systems.[17] Table 4 gives these and all the other ratios known to us for the thionoester/ester **15**,[21] the mesityl derivatives **16**,[18] the benzo[b]-2,3-dihydrothiophene-2-thione system **17**,[22] and the estimated value for the $MeC(=X)OR$ system.[20]

The much higher extent of thioenolization than of enolization is ascribed[34] to differences in bond energies. A rough estimate which is based on identical C—C and C—H bond energies in the ketone and thioketone or the C=C bond energies in the enol and thioenol and disregard the effect of the C=C bond on the O—H and S—H bonds is based on the following bond energies in kcal/mol: C—S, 61 S—H, 82, C=S, 115; C—O, 88, O—H, 110, C=O, 177.[35–38] From these values the thioenolization equilibrium is 7 kcal/mol more favored than the enolization, in agreement with the $K_{Thioenol}/K_{Enol}$ ratios of 10^4:10^6 in Table 4.

A drawback of this approach is that the O—H and S—H bond energies are those for saturated and not for vinylic systems. Indeed, for compounds like **14**, Ar = Ph, *p*-An, X=O, the O—H BDE is *ca.* 80 kcal/mol,[39] much lower than the value quoted above. Two approaches can circumvent this problem. First,[40] since the $\Delta H_f(PhX) - \Delta H_f(vinyl\text{-}X)$ difference is almost independent of X, the hypothetical reaction 5 (using experimental ΔH_f's),[41] where thiocamphor and camphor represent C=S and C=O species, is useful. The exothermic ΔH_f of 8.3 ± 1.2 kcal/mol, fits the values derived from the bond energies.

$$\begin{array}{lccccc} & \text{Thiocamphor} & + \text{PhOH} & \rightarrow & \text{Camphor} & + \text{PhSH} \\ \Delta H_f(\text{kcal/mol}) & -6.0 & -23.9 & & -63.9 & +26.6 \end{array} \quad = -8.3 \qquad (5)$$

The second approach is based on theoretical calculations. Extensive calculations[34] show that the differences in the enolization energies for $CH_3CH{=}X$, X = S, O depend on the level of theory, but thioenolization ($\Delta H = -5.5$–8 kcal/mol) is always favored over enolization ($\Delta H = 5$–7 kcal/mol). For $(CH_3)_2C{=}X$, the $\Delta\Delta H$ value is 8.8 kcal/mol at B3LYP/6-31G**. In less extensive calculations the $\Delta\Delta H$ values were 8–11 kcal/mol.[42]

For systems substituted by two strong EWGs the $K_{Thioenol}/K_{Enol}$ ratios differ from those in the first seven entries of Table 4.

Table 4. Collected literature pK_{Enol} and $pK_{Thioenol}$ values and $K_{Enol}/K_{Thioenol}$ ratios for various systems (X = O, S)

System	Solvent	pK_{Enol}	$pK_{Thioenol}$	$K_{Thioenol}/K_{Enol}$	Reference
$Ph_2C{=}C(Ar)XH$, **14** Ar = Ph	Hexane, DMSO-d_6	1.22[a]	≤ -2[b]	$\geq 10^6$[b]	[15, 16]
FlC(=X)OMe,[c] **15**	H_2O	[d]	5.80	10^4	[21]
MesC(=X)Me,[e] **16**	H_2O	6.92	0.94	10^6	[18, 19]
MeC(=X)OR	H_2O	18.5[f]	13.2[g]	$\geq 10^5$	[20]
, **17**	H_2O	3.62	−1.3	$\geq 10^5$	[22]
PhC(R)=C(XH)CH_2R, R = H, Ph		—	—	$\geq 10^6$	[16] [h]
(RR′CH)$_2$C=X, R = R′ = Me, R = H, R′ = *i*-Pr		—	—	$\geq 10^6$	[16] [h]
RNHC(=X)CH(CN)CONMe$_2$ R = *p*-An, Ph **3/5**	$CDCl_3$	−0.10 0.60	−0.57 −0.60	0.06 0.07	[13]
RNHC(=X)CH(CN)CONHMe R = *p*-An, Ph **3/5**	$CDCl_3$	0.95 0.95	1.15 1.10	1.57 1.39	[13]
RNHC(=X)CH(CN)CONHMe R = *p*-An, Ph **3/5**	THF-d_8	0.72 0.72	−0.57 −0.44	0.05 0.07	[13]
RNHC(=X)CH(CN)CONHMe R = *p*-An, Ph **3/5**	CD_3CN	0.12 −0.03	−0.68 −0.68	0.16 0.19	[13]
RNHC(=X)CH(CN)CONHMe R = *i*-Pr, *t*-Bu **3/5**	$CDCl_3$	1.06 0.72	−0.32 −0.32	0.04 0.09	[13]
RNHC(=X)CH(CN)CONH$_2$ R = *i*-Pr, *t*-Bu **3/5**	$CDCl_3$	−1.7 −1.7	−0.38 −0.54	$\leq$0.008 $\leq$ 0.07	[13]
i- PrNHC(=X)CH(CN)CONHPr-*i* **3/5**	$CDCl_3$	0.91	−0.49	0.04	[13]

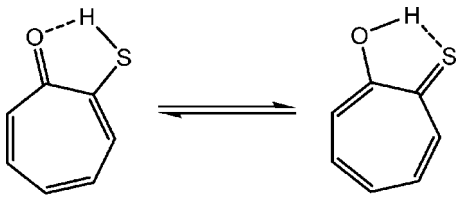
[a] Estimated in hexane.
[b] In DMSO-d_6.
[c] Fl = Fluorenyl.
[d] Value not given, the ratio is estimated in Reference [21].
[e] Mes = Mesityl.
[f] R = OMe.
[g] R = SEt.
[h] Data estimated in Reference [16] from literature data.

Comparing the $K_{Thioenol}$ values of the cyano monothiocarbonylmalonamides **5** with the K_{Enol} values for cyano malonamides **3** give substituent and solvent-dependent $K_{Thioenol}$(**5**)/K_{Enol}(**3**) ratios. As shown in the last seven entries of Table 4 the ratios are mostly < 0.2 and only two of them are 1.4–1.6.

Considering the approximate agreement between the values based on the extensive calculations and the bond energy calculations and the first entries of Table 4, it could be expected that the comparisons in Table 3 will give similar results. The strong effect of the EWGs on both the amides and the thioamides caused a 'complete' enolization (within the limit of detection of < 1–2% of one of the species by our NMR method), for **10a–c**/**11a–c** and **8a–b**/**9a–b**, whereas **8c**/**9c** in DMSO-d_6 gave the enolate anion. However, disregarding other data for the **8**/**9** systems in DMSO-d_6 since enolate ion may also be formed, $K_{Thioenol}/K_{Enol}$ for **8g**/**9g–10g**/**11g** is *ca.* 0.01 in $CDCl_3$, still small in CD_3CN and is *ca.* 0.2 for **8i**/**9i–10i**/**11i**. Consequently, for the limited data available the values of < 1 are lower than those in the top entries of Table 4. They roughly resemble those at the bottom of Table 4 for systems activated by two EWGs.

The significant differences in $K_{Thioenol}/K_{Enol}$ ratios for compounds substituted and unsubstitted by EWGs may be due either to (i) the fact that our systems are thioenols of carboxylic acid amides, (ii) to the presence of the two EWGs, or (iii) to the presence or absence of hydrogen bonds of different strengths. Since the ratios for carboxylic esters and thionoesters lead to the high $K_{Thioenol}/K_{Enol}$ ratios characteristic of 'simple' ketones and thioketones shown in Table 4, so that, for example, $Ph_2CHC(=S)OR$ undergoes complete thioenolization whereas the oxygen analog does not enolize,[43] explanation (i) is excluded. Explanation (ii) seems to contribute to the different ratios. The data of Table 1 show an extensive change in bond lengths, especially in elongation of C(1)—C(2), caused by the two EWGs (*cf.* structure **1b**). Since bond lengths are correlated with their strengths, we believe that the calculations mentioned above, which are approximately applicable to the unactivated systems, should not necessarily apply to systems activated by EWGs. We note however that the C=C bond elongation is the same in both the thioenol **11a** and the enol **9a** (Table 1).

Intramolecular hydrogen bonds are absent in the systems unactivated by EWGs, but S—H···O and O—H···O bonds are present in the β-ester activated systems. The importance of the O—H···O *versus* O—H···S and O···H—S hydrogen bonds is demonstrated in the thioenol/enol equilibrium in the 2—SH-substituted tropone system **18a**. The equilibrium with the enol 2-OH-tropothione **18b** (Eqn (6)) was reported to favor **18b** in solution[44] and in the solid.[45] This indicates that in a direct enol/thioenol competition the enol with the O—H···S hydrogen bond is favored over the thioenol with an S—H···O hydrogen bond.



18a **18b**

However, structure **18a** is stabilized by O—H···O hydrogen bonds with $[Ph_2C(OH)C{\equiv}C]_2$ in a 2:1 clathrate,[46] with O···O distances of 2.824 Å. Hence, an O—H···O bond is preferred

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over an O···H—S bond. This should decrease the $K_{Thioenol}/K_{Enol}$ ratios. We conclude that explanations (ii) and (iii) account qualitatively for the $K_{Thioenol}/K_{Enol}$ ratios.

Comparison of the solid state structures of Meldrum's acid derivatives of the enol 9a, R = Ph and the thioenol *11a*

The C(1)—C(2) bond lengths of 1.426 (5) Å in **9a**, R = Ph[1] and the almost identical 1.425 (3) Å in **11a** (Table 1) are longer than a normal C=C double bond, but shorter than a single C—C bond (see below). The C(4)—O(2) bond of 1.229 (4) Å for **11a** is 0.011 Å shorter than for **9a**, R = Ph[1], and this is ascribed to a weaker O···H—S than O···H—O hydrogen bond. The corresponding C(3)—O(1) bond difference is just 0.001 Å, indicating a similar O···H—N hydrogen bonding for both derivatives. In both of them the C(4)—O(2) bond is longer than the C(3)—O(1) bond due to stronger C=O···H—O and C=O···H—S than C=O···H—N hydrogen bonds. As expected, the O—H and O···H lengths are shorter than the respective S—H and S···H lengths and angle < OHS is ≪OHO, while the <NHN angles are closer (Table 1). The C(2)C(4)O(2) angle for the thio derivative is 127.1°, 10.2° larger than for the oxo derivative with the stronger C=O···H—O hydrogen bond, while the C(2)C(3)O(1) angles are almost identical (126.52° for **11a** and 126.1° for **9a**, R = Ph), because of the similar N—H···N bonds. Most of the angles around the C(1)—C(2) bond are close to 120° (Table 1). We conclude that both derivatives are enolic and that the hydrogen bond in the thioenol is weaker than in the enol.

In the up to August 2007 version of CSD we found X-ray structures of only 5 non-aromatic compounds with the C=C—S—H moiety derived from thioketones. These include (i) a clathrate of two molecules of 2-monothiotropone associate hydrogen bonded to 1,1,6,6-tetraphenylhaxa-2,4-diyne-1,6-diol with a **C=C**—S bond length of 1.384 Å and a S—H···O hydrogen bond;[46] (ii) dithiotropone with **C=C**—S bond length of 1.389 Å and an unsymmetrical S—H···S hydrogen bond;[47] (iii) (3,4,5-triphenyl-3,4-dihydro-2H-thiopyran-2-ylidene)methanethiol with a C=C—S bond length of 1.338 Å;[48] (iv) *N*-phenyl-2,3-dithiomaleimide, a dithioenol having a O=C—**C**(SH)=**C**(SH)— moiety, with a C=C—S bond length of 1.327(8) Å;[49] (v) triphenylethenethiol, with a **C=C**—S bond length of 1.356(5) Å.[15]

Consequently, all the C=C bond lengths in these cases are < 1.389 Å, compared with the bond length of 1.425 Å for **11a**. This difference reflects the effect of conjugation of the C=C bond with additional C=C bonds, phenyl group, or a single EWGs in systems (i)–(v), compared with the much stronger delocalizing ability of the two β-EWGs in **11a** which is reflected in contributing structure **1b**. **11a** is therefore a record holder of the C=C bond length among the known thioenols.

The δ(SH) values and the relative strengths of the O····H—O, O····H—S, and O····H—N hydrogen bonds served as probes for the thioenol structures. Both intermolecular and intramolecular competition between enolization and thioenolization in thioamides substituted by two β-EWGs shows that enolization is more extensive than thioenolization, in contrast to simple ketones and thioketones in which thioenolization is favored over enolization by large factors.

The solid state structure of the 5-anilido-MA derivative **11a** is the first X-ray structure of a noncyclic thioenol of a thioamide activated by two β-EWGs and the doubly hydrogen bonded system with S1—H···O2 and N1—H···O1 moieties can serve as a model for activated thioenols. Comparison of the solid state structures of MA-substituted thioenol and enol show a stronger hydrogen bond in the enol than in the thioenol.

EXPERIMENTAL

General methods

Melting points, ^{1}H and ^{13}C NMR and IR spectra were measured as described previously.[50] All the commercial precursors and solvents were purchased from Aldrich.

*Reaction of Meldrum's acid with phenyl, 1-naphthyl, and isopropyl isothiocyanates to form **11a–c***

To a mixture of MA (0.72 g, 5 mmol) and triethylamine (1.5 ml, 10 mmol) in dry DMF (5 ml), 1-naphthyl isothiocyanate (926 mg, 5 mmol) was added. The mixture was stirred at room temperature (RT) for 4 h, poured into an ice-cold 6% HCl solution (100 ml) and the yellow solid formed was filtered and washed with cold water, giving 1.45 g (88%) of the thioenol of 5-(1-naphthylaminothiocarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **11b**, mp 150–151 °C (dec). Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 62.01; H, 4.56; N, 4.26. Found: C, 62.20; H, 4.53; N, 4.50. ^{1}H NMR ($CDCl_3$, 298 K, 400 K) δ: 1.81 (6H, s, Me), 7.51–7.60 (3H, m, Ar-H), 7.83–7.95 (4H, m, Ar-H), 11.44 (1H, s, NH), 13.16 (1H, s, SH). ^{13}C NMR ($CDCl_3$) δ: 26.39 (q, J = 128.7 Hz, Me), 83.44 (s, C_β), 103.40 (m, J = 4.8 Hz, CMe_2), 121.89, 125.08, 125.13, 126.98, 127.54, 128.31, 129.00, 129.48, 132.32, 134.27, 165.65(C=O), 167.59(C=O), 179.79 (C_α).

The thioenol of 5-(1-phenylaminothiocarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **11a**, mp 113–114 °C, was similarly obtained in 2.21 g (79%) from MA (1.44 g, 10 mmol) and phenyl isothiocyanate (1.2 ml, 10 mmol). The thioenol of 5-(1-isopropylaminothiocarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **11c**, mp 100–102 °C, was obtained in only 13% yield (0.33 g) from MA (1.44 g, 10 mmol) and isopropyl isothiocyanate (1.08 ml, 10 mmol). Spectral and analytical data are given in Tables S1–S3 in the Supplementary data.

*The thioenols (**11e**) of methyl (1-naphthylaminothiocarbonyl) cyanoacetate (**10e**), and (**11d**) of methyl 1-phenylaminothiocarbonyl) cyanoacetate (**10d**)*

To a stirred mixture of methyl cyanoacetate (0.25 g, 2.5 mmol) and dry Et_3N (0.75 ml, 5 mmol) in dry DMF (3 ml), 1-naphthyl isothiocyanate (463 mg, 2.5 mmol) was added and the mixture was stirred for 24 h at RT giving a white solid. The solid was filtered and washed with dry ether, giving 0.68 g (71%) of the ammonium salt of **11e** $[C_{15}H_{11}N_2O_2S]^-Et_3N^+H$. ^{1}H NMR (DMSO-$d_6$, 298 K, 400 Hz) δ: 1.16 (9H, t, J = 7.3 Hz, CH_3CH_2N), 3.08 (6H, q, J = 7.3 Hz, CH_3CH_2N), 3.62 (3H, s, OMe), 7.46 (1H, t, J = 7.7 Hz, Ar-H), 7.49–7.56 (2H, m, Ar-H), 7.69 (1H, d, J = 8.5 Hz, Ar-H), 7.92 (1H, d, J = 7.3 Hz, Ar-H), 7.98 (1H, d, J = 8.1 Hz, Ar-H), 8.25 (1H, d, J = 7.3 Hz, Ar-H), 8.82 (1H, br s, [Et_3NH]), 12.25 (1H, s, NH). A solution of the salt in DMF (5 ml) was added dropwise during 10 min to a stirred ice-cold 6% HCl solution (5.0 ml). The pure white precipitate formed was filtered, washed with cold water (100 ml) and dried to give 0.43 g (60%) of **10e**, mp 139–140 °C. Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.38; H, 4.23; N, 9.86. Found: C, 63.47; H, 4.26; N, 10.09. ^{1}H NMR ($CDCl_3$, 298 K, 400 K) δ: 3.87 (3H, s, OMe), 4.61 (1H, s, SH), 7.49 (1H, d, J = 7.3 Hz, Ar-H), 7.53 (1H, t, J = 8.0 Hz, Ar-H), 7.56–7.64 (2H, m, Ar-H), 7.87–7.96 (3H, m, Ar-H),

11.91 (1H, s, NH). ^{13}C NMR: 51.95 (q, $J = 147.9$ Hz, Me), 72.62 (s, C_β), 127.16, 127.72, 128.51, 129.38, 129.53, 133.04, 134.26, 168.24, 170.72.

The phenyl derivative **11d**, mp 132–133 °C, was similarly obtained in 53% yield, but no ammonium salt was obtained in the first step. Spectral and analytical data are given in Tables S1–S3 in the Supplementary data.

*The thioenol (**11f**) of 2,2,2-trichloroethyl (1-phenylaminothiocarbonyl) cyanoacetate (**10f**)*

A mixture of 2,2,2-trichloroethyl cyanoacetate (0.54 g, 2.5 mmol), dry Et_3N (0.75 ml, 5 mmol), and phenyl isothiocyanate (0.3 ml, 2.5 mmol) in DMF (5 ml) was stirred for 1 h at RT, and poured into an ice-cold 6% HCl solution (50 ml). The oily solid obtained solidified on cooling overnight in a refrigerator, giving 0.46 g (52%) of **10f** as a yellow solid, mp 130–131 °C. Anal. Calcd for $C_{12}H_9Cl_3N_2O_2S$: C, 40.97; H, 2.56; N, 7.97. Found: C, 41.27; H, 2.64; N, 8.04. ^{1}H NMR ($CDCl_3$, 298 K, 400 K) δ: 4.83 (1H, s, SH), 4.86 (2H, s, CH_2), 7.29 (2H, d, $J = 8.1$ Hz, Ph-H), 7.40–7.51 (3H, m, Ph-H), 11.48 (1H, s, NH). Spectral and analytical data are given in Tables S1–S3 in the Supplementary data.

*Bis(2,2,2-trifluoroethyl) (1-phenylaminothiocarbonyl)malonate (**10g**) and bis(2,2,2-trifluoroethyl) (1-naphthylaminothiocarbonyl)malonate (**10h**)*

To a stirred mixture of bis(2,2,2-trifluoroethyl)malonate (1.34 g, 5 mmol) and dry triethylamine (1.5 ml, 10 mmol) in dry DMF (10 ml), phenyl isothiocyanate (0.6 ml, 5 mmol) was added and the stirring continued overnight at RT. The solution was added dropwise with stirring into an ice-cold 6% HCl solution (100 ml) and the yellow precipitate was filtered, washed with cold water and dried in air to give 0.89 g (68%) of **10g/11g**, mp 75–76 °C. Anal. Calcd for $C_{14}H_{11}F_6NO_4S$: C, 41.69; H, 2.73; N, 3.47. Found: C, 41.16; H, 3.12; N, 3.45.

^{1}H NMR ($CDCl_3$, 298 K, 400 K) Thioamide **10g** (94%) δ: 4.51–4.75 (4H, m, CH_2CF_3), 5.31 (1H, s, CH), 7.31 (t, $J = 7.6$ Hz), 7.43 (t, $J = 8.0$ Hz), 7.70 (d, $J = 8.0$ Hz), 10.33 (1H, s, NH). Thioenol **11g** (6%): 4.34–4.52 (0.25 H, m, CH_2CF_3), 4.95 (0.07 H, s, SH), the phenyl signals overlap the **9g** signals, 12.24 (0.07 H, s, NH).

The 1-naphthyl derivative **10h**, mp 78–80 °C, was similarly obtained in 79% yield. Spectral and analytical data are given in Tables S1–S3 in the Supplementary data.

*Dimethyl (1-phenylaminothiocarbonyl)malonate (**10i**)*

Dimethyl malonate (2.64 g, 20 mmol) in dry THF (20 ml) was added dropwise with stirring during 10 min to a dispersion of Na (0.48 g, 21 mmol) in dry THF (50 ml). On stirring overnight, all the Na reacted. Phenyl isothiocyanate (2.4 g, 20 mmol) in dry THF (30 ml) was added dropwise to the stirred mixture during 30 min and the mixture was refluxed for 3 h. The solvent was evaporated, the remaining sodium salt was dissolved in DMF (5 ml) and the solution was poured into ice-cold 6% HCl solution (100 ml) with stirring. The oily product obtained was extracted with a 4:1 hexane/ether mixture (300 ml), washed with ice-cold water (3×100 ml) and dried (Na_2SO_4). The solvents were evaporated under reduced pressure, leaving 2.83 g (53%) of **10i** as a red, heavy oil. Anal. Calcd for $C_{12}H_{13}NO_4S$: C, 53.93; H, 4.87; N, 5.24. Found: C, 53.49; H, 5.01; N, 5.54. ^{1}H NMR ($CDCl_3$, 298 K, 400 K) δ: 3.74 (6H, s, Me), 5.05 (1H, s, CH), 7.18 (1H, t, $J = 7.7$ Hz), 7.31 (2H, t, $J = 7.7$ Hz), 7.70 (2H, d, $J = 8.0$ Hz), 10.68 (1H, s, NH). Spectral and analytical data are given in Tables S1–S3 in the Supplementary data.

SUPPLEMENTARY DATA

Tables S1 and S2 with complete ^{1}H and ^{13}C NMR data and Table S3 with analytical data are available online. The full crystallographic data for compound **11a** is given as a *cif*.

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