Enols and thioenols of substituted cyanomonothiocarbonylmalonamides: structures, enolization *vs.* thioenolization, equilibria and conformations†‡§

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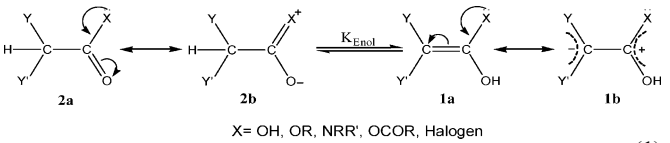
Condensation of organic isothiocyanates with cyanoacetamides gave 24 *N*- and *N*′-substituted cyanomonothiocarbonylmalonamides in different tautomeric ratios *i.e.*, amide–thioamides (TMA) $R^3NHCSCH(CN)CONR^1R^2$ (**12**), thioamide–enols of amides (E) $R^3NHCSC(CN)=C(OH)NR^1R^2$ (**11**) or amide–thioenols (TE) $R^3NHC(SH)=C(CN)CONR^1R^2$ (**13**). The equilibrium constants ($K_{thioenol}$ = [TE]/[TMA] and K_{enol} = [E]/[TMA]) in solution depend on R^1, R^2, R^3 and the solvent. The %(E + TE) for NR^1R^2 increases in the order $NMe_2 < NHMe < NH_2$. The ($K_{thioenol} + K_{enol}$) in various solvents follows the order $CCl_4 > CDCl_3 > C_6D_6 > THF\text{-}d_8 > (CD_3)_2CO > CD_3CN > DMF\text{-}d_7 > DMSO\text{-}d_6$. The δ(OH) values are 16.46–17.43 and the δ(SH) values are 3.87–5.26 ppm in non polar solvents, *e.g.*, $CDCl_3$ and 6.34–6.97 ppm in THF-d_8 and CD_3CN. An intramolecular O–H ⋯ O hydrogen bond leads to the preferred *Z*-configuration of the enols, and an N–H ⋯ O bond stabilizes the thioenols' preferred *E*-configuration with a non-bonded SH in solution. X-Ray crystallography revealed that systems with high %(E + TE) in solution mostly display the enols **11** in the solid state and systems with lower %(E + TE) in solution display structure **12**. The differences in δ(OH), δ(NH), K_{enol} and crystallographic data for analogous enol and thioenol systems are compared.

Introduction

Enols and keto–enol equilibria for mono-carbonyl and 1,3-dicarbonyl compounds have been extensively investigated over the last hundred years.[1] In contrast, enols of carboxylic acids, their esters, anhydrides, amides, thioamides or halides have been scarcely investigated until recently.[2] In the last decade we have extensively investigated these species,[3,4] especially the enols of amides,[3a–c,4] which are usually unobservable, *i.e.*, the equilibrium constant K_{enol} = [enol]/[amide] is <0.01. The computed K_{enol} for acetamide is $10^{-21.6}$.[5] The reason for this is that mesomeric electron donation by X stabilizes the acid derivative **2a** *via* contributing structure **2b** which is favored by the negative charge on its oxygen atom (eqn (1)).



(1)

A similar electron donation by X and OH to C_α of the enol **1a** creates a negative charge on C_β, which only slightly stabilizes the enol when Y,Y′ are not electron-withdrawing groups (EWGs). Consequently, the acid derivative is much more stabilized than the enol with a drastic reduction in K_{enol} compared with those for simple carbonyl derivatives.[6]

Our approach to stabilized enols of carboxylic acid derivatives is by increased stabilization of structure **1b** by substituting C_β with resonatively negative charge EWGs Y and Y′.[3,4] The stabilized **1b** is zwitterionic with delocalized positive charge on C_α, X and OH and negative charge on C_β, Y and Y′. This implies a relatively long C_α–C_β formal double bond with a significant single bond character. The acid derivatives are presumably also destabilized by Y,Y′/CO dipole–dipole repulsion.[3b]

By applying this approach we observed by NMR spectroscopy >100 enols of amides YY′C=C(OH)NHX (**4**) either exclusively or as mixtures with the isomeric amides Y′YCHCONHX (**3**) in solution, and determined the solid structures of >25 enols by X-ray crystallography. Combinations of Y,Y′ for which only the enol is observed in $CDCl_3$ ($K_{enol} \geq 50$) include amides where Y′Y is the cyclic diester Meldrum's acid (MA) moiety,[3a] Y = CN, Y′ = CO_2R, R = CH_3[3b] or CH_2CCl_3,[4d] or Y = $CO_2CH(CF_3)_2$, Y′ = $CO_2CH_2CF_3$. The K_{enol} value is low when Y = Y′ = CO_2Me.[3a]

A problem is that Y or Y′ can serve as an enolization site. Although ester groups do not compete with an amide, a ketonic CO at C_β, *e.g.*, in PhNHCOCH(*COMe*)CO_2Et (**5**),[3b] serves as an enolization site. Substituted 2-amidoindandiones can form enol isomers on both the amide and the ring CO.[7]

Cyanomalonamides display in solution both the amide **6** and one of the enols **7**or **8** (eqn (2)). The enolic hydrogen forms a strong intramolecular hydrogen bond to the carbonyl of the second amide group and apparently migrates rapidly between the two oxygens.[8] The K_{enol} and δ_H (OH) values in moderate and polar solvents are relatively high.

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$R^1R^2NCOCH(CN)CONHR^3 \rightleftharpoons R^1R^2NCOC(CN)=C(OH)NHR^3$ or $R^1R^2NC(OH)=C(CN)CONHR^3$

6 **7** **8**

a: $R^1 = R^2 = Me$; $R^3 = Ph$, *p*-$MeOC_6H_4$, C_6F_5, i-Pr, *t*-Bu (K_{Enol} ($CDCl_3$) = 2.2-4.0)
b: $R^1 = Me$, $R^2 = H$; $R^3 = Ph$, *p*-$MeOC_6H_4$, C_6F_5, i-Pr, *t*-Bu (K_{Enol} ($CDCl_3$) = 5.3-11.5)
c: $R^1 = R^2 = H$; $R^3 = Ph$, *p*-$MeOC_6H_4$, C_6F_5, i-Pr, *t*-Bu (K_{Enol} ($CDCl_3$) ≥ 50)
d: $R^1 = H$, $R^2 = R^3$ = i-Pr (K_{Enol} ($CDCl_3$) = 8.09) (2)

$CH_2(CN)CONR^1R^2$ + R^3NCS
9 **10**
↓ Na/dry THF

$R^3NHCSC(CN)=C(OH)NR^1R^2 \overset{K_{enol}}{\rightleftharpoons} R^3NHCSCH(CN)CONR^1R^2 \overset{K_{thioenol}}{\rightleftharpoons} R^3NHC(SH)=C(CN)CONR^1R^2$

Enol (E)	Amide/Thioamide (TMA)	Thioenol (TE)
11	**12**	**13**
11a: $R^1 = R^2 = Me$; $R^3 = Ph$	**12a**	**13a**
11b: $R^1 = R^2 = Me$; R^3 = *p*-$MeOC_6H_4$	**12b**	**13b**
11c: $R^1 = R^2 = Me$; R^3 = 1-Np (1-Naphthyl)	**12c**	**13c**
11d: $R^1 = R^2 = Me$; $R^3 = Me$	**12d**	**13d**
11e: $R^1 = R^2 = Me$; $R^3 = Et$	**12e**	**13e**
11f: $R1 = R^2 = Me$; R^3 = i-Pr	**12f**	**13f**
11g: $R^1 = R^2 = Me$; R^3 = *t*-Bu	**12g**	**13g**
11h: $R^1 = H$; $R^2 = Me$; $R^3 = Ph$	**12h**	**13h**
11i: $R^1 = H$; $R^2 = Me$; R^3 = *p*-$MeOC_6H_4$	**12i**	**13i**
11j: $R^1 = H$; $R^2 = Me$; R^3 = 1-Np	**12j**	**13j**
11k: $R^1 = H$; $R^2 = Me$; $R^3 = Me$	**12k**	**13k**
11l: $R^1 = H$; $R^2 = Me$; $R^3 = Et$	**12l**	**13l**
11m: $R^1 = H$; $R^2 = Me$; R^3 = i-Pr	**12m**	**13m**
11n: $R^1 = H$; $R^2 = Me$; R^3 = *t*-Bu	**12n**	**13n**
11o: $R^1 = R^2 = H$; $R^3 = Ph$	**12o**	**13o**
11p: $R^1 = R^2 = H$; R^3 = *p*-$MeOC_6H_4$	**12p**	**13p**
11q: $R^1 = R^2 = H$; R^3 = 1-Np	**12q**	**13q**
11r: $R^1 = R^2 = H$; R^3 = i-Pr	**12r**	**13r**
11s: $R^1 = R^2 = H$; R^3 = *t*-Bu	**12s**	**13s**
11t: $R^1 = H$; R^2 = i-Pr; $R^3 = Ph$	**12t**	**13t**
11u: $R^1 = H$; $R^2 = R^3$ = i-Pr	**12u**	**13u**
11v: $R^1 = H$; $R^2 = CHPh_2$; R^3 = i-Pr	**12v**	**13v**
11w: $R^1 = H$; $R^2 = CHPh_2$; R^3 = *t*-Bu	**12w**	**13w**
11x: $R^1 = H$; $R^2 = Ph$; R^3 = *t*-Bu	**12x**	**13x**

(3)

In the present work we replaced one carbonyl group in **6** by a thiocarbonyl group, obtaining cyanomonothiocarbonylmalonamides $R^3NHCSCH(CN)CONR^1R^2$, in order to investigate the following goals: (i) to extend the scope of stable enols of amides with a β-thioamido group; (ii) to study the intramolecular competition between amide and thioamide enolization sites as a function of R^1–R^3; (iii) to probe the role of hydrogen bonding on the configuration and conformation of the enols and thioenols; (iv) to determine the solid state structure of these species, and whether it is the same as in solution.

Results

Synthesis

The 24 "formal"[9] cyanomonothiocarbonylmalonamides **11/12/13** (**a**–**x**) were prepared by reacting the anion of a substituted cyanoacetamide (**9**) with an organic isothiocyanate (**10**) (eqn (3)). The products are the amide–thioamide (TMA, **12**), the enol (E, **11**) and/or the thioenol (TE, **13**), or a mixture. Three equilibrium constants are defined: K_{enol}, $K_{thioenol}$ and K_{total} (eqn (4)). Compounds, **12e**,[10a] **12h**,[10b] **12k**,[10c] **11k**,[10c] **11o**,[10d] **11p**[10e,f] and **12r**[11] were prepared previously. The stereochemistries of **11** and **13** are discussed below. Compounds **11/12/13** are much more reactive than **6/7/8**. Several of them react on crystallization in a variety of ways, mostly to give heterocyclic compounds.[11]

$$K_{enol} = [E]/[TMA],\ K_{thioenol} = [TE]/[TMA],$$

$$K_{total} = ([E] + [TE])/[TMA] \quad (4)$$

Solid state structures

Solid state structures of eight systems were determined by X-ray diffraction.‡ Four of them display the enol structures **11h–11k**. **11h** and **11i** were crystallized from EtOAc and **11j** was crystallized from EtOAc under nitrogen. Fig. 1a displays the ORTEP drawing of **11j** which shows both intramolecular O–H···S and intermolecular CN···H–N hydrogen bonds. The four derivatives **12d** (Fig. 1b), **12f**, **12k**, **12v** display amide structures. **12d**, **12f** and **12v** were crystallized from $CDCl_3$.

Table 1 gives selected crystallographic data for enols **11h–11j**. Data for **11k**, which was crystallized from $CDCl_3$, was reported earlier.[10c] The differences between the relevant parameters for the four compounds are small, considering the standard deviations. The C(1)–O(1) bond lengths of 1.301–1.307 Å, the C(2)–C(4) bond of 1.402–1.417 Å, the small difference of ≤ 0.011 Å between the bond lengths of C(1)–C(2) and C(2)–C(3) for the three compounds, and the doubly bonded C=S moiety (1.687–1.700 Å), indicate a highly delocalized enol structure. The variable O–H bond length of 0.98–1.18 Å is in line with the difficulty in locating hydrogens by X-ray diffraction. The O···S non-bonding distance of 2.836–2.865 Å, and the non-linear C=S···H–O hydrogen bond of

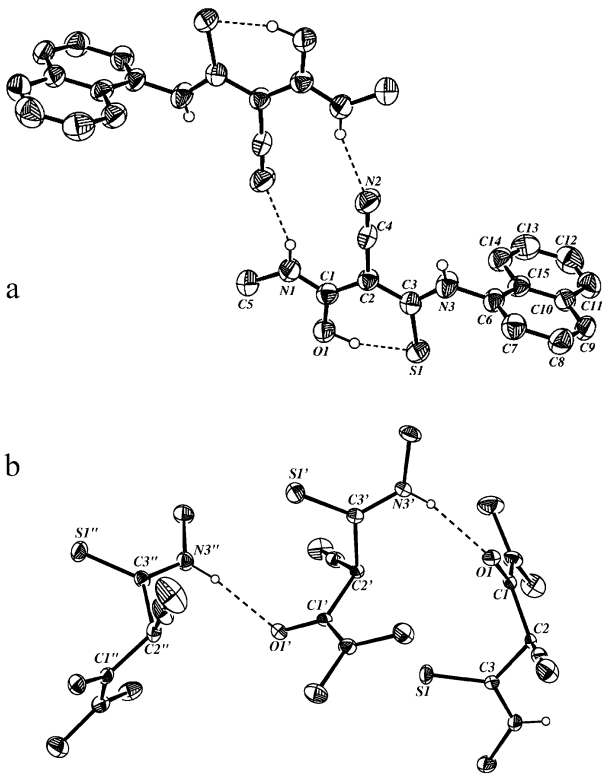

Fig. 1 ORTEP drawing of (a) **11j** and (b) **12d** (thermal ellipsoids scaled to include 50% probability).

1.70–1.93 Å indicate a weaker hydrogen bond than the O···H–O bond in enols **7**/**8**.[8] Bond angles around the C(1)–C(2) bond are 120 ± 5° (Table 1), and their sum of 359.8–360.0° indicate planarity around C(2). The structures are dimeric: one cyano nitrogen in each molecule is intermolecularly hydrogen bonded to the amide H–N–CO of a second molecule. These bonds cause a C(4)–N(2) bond elongation from 1.136–1.137 Å for the $C_{sp^1}{\equiv}N$ bond[12] to 1.148–1.151 Å. The non-bonding N···N# (N# belongs to a second molecule) and H···N# distances, the N–H bond lengths and the N(1)–H···N(2)# angles indicate an asymmetric and bent intermolecular hydrogen bond.

Fig. 1b, Table 2 and the ESI§ give structural data for the amides **12d**, **12f** and **12v** and of the "amide" part of **12r** (see below; those of **12k** was reported earlier[10c]), with normal bond lengths: C=O 1.228–1.236 Å, C=S 1.646–1.659 Å, C≡N 1.129–1.137 Å and C(1)–C(2) 1.535–1.543 Å. The 107.6–113.6° angles around C2 indicate an sp^3 carbon. The structures are "polymeric" where the C=O carbonyl is intermolecularly hydrogen bonded to the H–N–C=S of another molecule.

Crystallization of **12r** from CD_3CN gave an associate with an "apparent" amide structure **12r** intermolecularly hydrogen bonded *via* one water molecule to 3,5-bis(isopropylamino)-[1,2]dithiolane-4-carbonitrile (Fig. 1 in ref. 11). The C(1)–C(2), C(2)–C(3) and C(2)–C(4) bonds of **12r** are shorter, and the C(1)–O(1), C(3)–N(3) and C(4)–N(2) bonds are longer, than those of the other amides (Table 2). The H–N–C=S is intramolecularly hydrogen bonded to the C=O group with an N–H bond length and O···H and O···N distances of 0.82(2) Å, 2.01(2) Å and 2.667(2) Å, respectively, and an OHN angle of 137.7(17)°. It was suggested that the species is a radical derived from **12r**.[11]

System **11k**/**12k**/**13k**, R^3 = Me was crystallized either as the amide **12k** or as the enol **11k**, depending on the solvent polarity.[10c]

Structures in solution. NMR spectra and K_{enol} values in solution

^1H and ^{13}C NMR spectra were recorded for **11**/**12**/**13** in several solvents. Selected ^1H spectral parameters are given in Table 3 and the complete data are in Table S1. The ^{13}C NMR data are in Table S2 in the supplementary data.§

On dissolving a sample of the X-ray analyzed crystals of either **11** or **12** or the formal[9] TMA, the substituent- and solvent-dependent spectra of the tautomeric system **11** (E)/**12** (TMA)/**13** (TE) were instantaneously observed. The composition did not change with time, *i.e.*, equilibria between the various species is rapidly established, as found for other enols of amides.[3,4]

Both the E and TE species can *a priori* exist in both *E* and *Z* configurations. For the analogous **7**/**8** only the isomer whose enolic OH is intramolecularly hydrogen bonded to the *cis* amido carbonyl is usually observed.[8] The linear CN cannot form an intramolecular CN···H–O hydrogen bond and the isomer with the *cis*-CN/OH configuration is not observed.

For all enols **11** the δ(OH) signals at >16 ppm in $CDCl_3$ indicate the presence of hydrogen bonding. Most derivatives (except for NR^1R^2 = NMe_2, R^3 = Alk) also showed a relatively high field singlet at *ca.* 3.9–7.0 ppm ascribed to a non-hydrogen bonded SH group of **13**.

Fig. 2a displays the low field region of a $CDCl_3$ solution of formal[9] *t*-BuNHCSCH(CN)CONHMe **12n**. The lowest field very narrow doublet at δ 16.88 is ascribed to the hydrogen bonded OH signal of **11**, by analogy with many systems.[3,4] There are two relatively sharp NH signals for each species, with reliable position and integration for assignment and for determination of the K_{enol} values; *e.g.*, the signals at δ 6.55 and 6.05 with 99% intensities of the δ(OH) are the NH signals of **11**. The NH signals at δ 11.61 and 5.81 with 40 ± 1% intensity of δ(OH), are ascribed to **13**. Its SH signal almost overlaps the amide CH signal at δ 4.79. The signals of **12** at δ 8.75 and 7.05 have 81% intensity of δ(OH).

The ^1H NMR spectrum in DMSO-d_6 displays only the CH, CSNH and CONH signals of **12n** at δ 5.13, 8.00 and 9.77 ppm, respectively (Fig. 2b). In the ^{13}C NMR spectrum in $CDCl_3$ (Fig. 2c), three pairs of signals appear in the high ppm region: at *ca.* δ 185 for the C=S groups of **11n** and **12n**, at δ 172 and 168 for C_α of the **11n** and **13n**, and at δ 162 and 164 for the C=O signals of **13n** and **12n**. The coupled C_β signals are singlets at 66.7 (**11n**) and 70.7 (**13n**) ppm and a doublet at 56.1 ppm for **12n**. Simpler ^1H NMR spectra are observed for systems **11a–g**/**12a–g**/**13a–g**, having only three NH signals; *e.g.*, for **11c**/**12c**/**13c** the δ(NH) values resemble those observed in Fig. 2a. The separated CH and SH signals are at 5.49 and 4.50 ppm, respectively.

The δ(OH), δ(SH) and δ(CH) for selected $R^3NHCSCH(CN)$-$CONR^1R^2$ systems in several solvents where all three species are observed are given in Table 3. In all the solvents and for all R's δ(OH) is at 16.46–17.43, δ(SH) is at 3.87–6.97 and δ(CH) is at 4.09–5.79. Changes due to combinations of R^1, R^2 and R^3 are not systematic. The highest δ(OH) and δ(SH) values are in THF-d_8 or C_6D_6, for each group.

In the δ_C values of the C=S, C=O, C_α(**11**), C_α(**13**), C≡N and C_β signals for the three isomers of all systems soluble in $CDCl_3$ (Table S3 in the ESI§), each isomer displays pairs of low field

Table 1 Selected crystallographic data (bond lengths, hydrogen bond distances and angles) for the enols $R^3NHCSC(CN)=C(OH)NR^1R^2$ **11h–11j**, (R^3 = Ph, *p*-An(*p*-$MeOC_6H_4$), 1-Np) at room temperature[a]

Compound	**11h** (R^3 = Ph)[b]	**11i** (R^3 = *p*-An)	**11j** (R^3 = 1-Np)
Bond length/Å			
C(1)–C(2)	1.426(2), 1.425(2)	1.424(5)	1.412(3)
C(1)–N(1)	1.318(2), 1.317(2)	1.314(4)	1.319(3)
C(1)–O(1)	1.301(2), 1.302(2)	1.301(4)	1.307(2)
C(2)–C(3)	1.427(2), 1.427(2)	1.427(4)	1.423(3)
C(3)–N(3)	1.352(2), 1.345(2)	1.346(4)	1.344(3)
C(3)–S(1)	1.693(1), 1.700(1)	1.687(3)	1.694(2)
C(2)–C(4)	1.415(2), 1.414(2)	1.402(5)	1.417(3)
C(4)–N(2)	1.151(2), 1.149(2)	1.151(4)	1.148(3)
O(1)–H(O1)	1.06(3), 1.05(3)	1.18(5)	0.98(3)
S(1)···H(O1)	1.85(3), 1.84(3)	1.70(5)	1.93(3)
O(1)···S(1)	2.857(1), 2.849(1)	2.836(3)	2.865(2)
N(1)–H(N1)	0.82(2), 0.77(2)	0.83(3)	0.87(2)
N(3)–H(N3)	0.75(2), 0.76(2)	0.83(4)	0.78(2)
N(2)···H(N1)[c]	2.23(2), 2.30(2)	2.23(4)[#1]	2.14(2)[#2]
N(1)···N(2)[c]	2.999(2), 2.975(2)	2.976(5)[#1]	2.947(3)[#2]
Bond angle/°			
O(1)–C(1)–C(2)	122.7(1), 123.0(1)	122.5(3)	122.9(2)
O(1)–C(1)–N(1)	115.3(1), 115.3(1)	115.4(3)	115.3(2)
N(1)–C(1)–C(2)	122.0(1), 121.7(1)	122.2(3)	121.8(2)
C(1)–C(2)–C(3)	124.9(1), 125.1(1)	124.9(3)	125.1(2)
C(1)–C(2)–C(4)	116.1(1), 116.3(1)	116.0(3)	116.7(2)
C(4)–C(2)–C(3)	118.9(1), 118.6(1)	119.0(3)	118.0(2)
C(2)–C(3)–S(1)	123.7(1), 122.9(1)	123.1(3)	124.2(2)
N(3)–C(3)–S(1)	120.5(1), 120.3(1)	119.8(3)	119.2(2)
C(2)–C(3)–N(3)	115.8(1), 116.7(1)	117.1(3)	116.7(2)
C(2)–C(4)–N(2)	178.5(2), 179.3(2)	179.3(5)	178.4(3)
C(1)–O(1)–H(O1)	108(2), 104(2)	104(2)	107(2)
O(1)–H···S(1)	156(2), 160(2)	161(3)	158(2)
N(1)–H(N1)···N(2)[c]	150(2), 151(2)	151(3)[#1]	153(2)[#2]

[a] Measured at 173(1) K. [b] Two independent molecules. [c] Symmetry transformations used to generate equivalent atoms: [#1], $-x+2, -y+1, -z+1$; [#2], $-x, -y+1, -z+1$.

Table 2 Selected crystallographic data for the amides $R^3NHCSCH(CN)CONR^1R^2$ [**12d**, **12f**, **12v**, **12r** (associated with a heterocycle)] at room temperature[a]

Compound	**12d** (R^3 = Me)	**12f** (R^3 = i-Pr)	**12v** (R^3 = i-Pr)	**12r** (R^3 = i-Pr)
Bond length/Å				
C(1)–C(2)	1.535(6)	1.542(2)	1.543(6)	1.447(2)
C(1)–N(1)	1.315(5)	1.310(2)	1.333(6)	1.340(2)
C(1)–O(1)	1.236(5)	1.229(2)	1.228(5)	1.253(2)
C(2)–C(3)	1.540(5)	1.544(2)	1.524(6)	1.425(2)
C(3)–N(3)	1.308(5)	1.315(2)	1.300(7)	1.333(2)
C(3)–S(1)	1.646(4)	1.659(1)	1.646(5)	1.713(2)
C(2)–C(4)	1.456(7)	1.467(2)	1.460(7)	1.418(2)
C(4)–N(2)	1.129(6)	1.137(2)	1.133(6)	1.149(2)
C(2)–H(C2)	0.98	0.98	0.98	—
N(3)–H(N3)	0.81(5)	0.82(2)	0.65(5)	0.82(2)
H(N3)···O(1)[b]	2.07(5)[#1]	2.15(2)[#2]	2.45(5)[#3]	2.01(2)[c]
N(3)···O(1)[b]	2.871(5)[#1]	2.910(2)[#2]	3.064(5)[#3]	2.667(2)[c]
Bond angle/°				
O(1)–C(1)–C(2)	118.8(4)	119.7(1)	122.6(5)	122.4(2)
O(1)–C(1)–N(1)	123.9(4)	122.7(1)	124.2(5)	119.0(2)
N(1)–C(1)–C(2)	117.3(4)	117.6(1)	112.9(4)	118.6(2)
C(1)–C(2)–C(3)	111.6(3)	112.3(1)	107.6(4)	124.9(1)
C(1)–C(2)–C(4)	109.9(4)	108.2(1)	110.2(4)	116.6(1)
C(4)–C(2)–C(3)	109.5(3)	107.7(1)	113.6(4)	118.5(1)
C(2)–C(3)–S(1)	121.0(3)	119.06(9)	120.8(4)	120.5(1)
N(3)–C(3)–S(1)	124.4(3)	126.9(1)	125.8(4)	121.4(1)
C(2)–C(3)–N(3)	114.6(4)	114.05(1)	113.1(4)	118.1(1)
C(2)–C(4)–N(2)	176.1(5)	177.7(2)	175.8(5)	174.9(2)
N(3)–H(N3)···(O1)[b]	172(5)[#1]	154(2)[#2]	158(7)[#3]	138(2)[c]

[a] Measured at 173(1) K. [b] Symmetry transformations used to generate equivalent atoms: [#1] $x-1, -y+1/2, z-1/2$; [#2] $x, -y+1/2, z+1/2$; [#3] $x, -y+2, z+1/2$. [c] The N–H is intramolecularly hydrogen bonded to oxygen O(1).

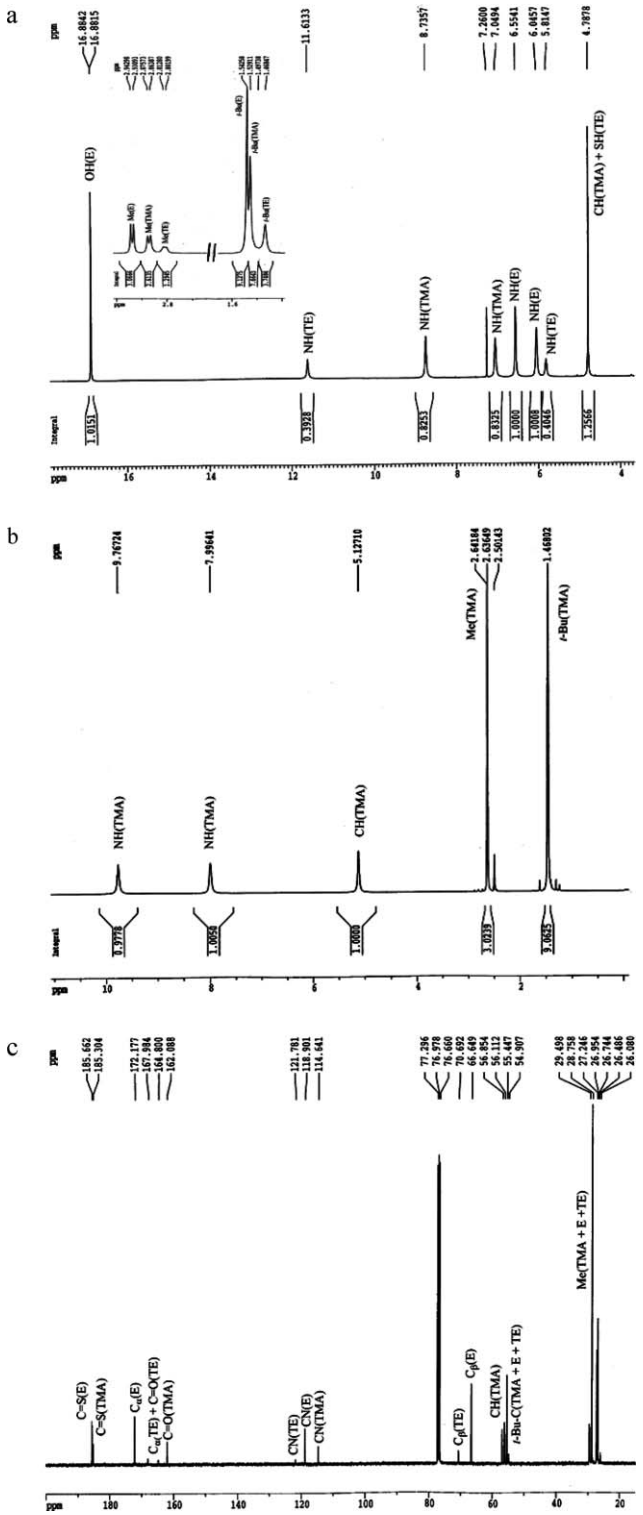

Fig. 2 ^{1}H NMR spectra for the **11n/12n/13n** system: (a) OH, NH, CH and SH regions (inset Me and *t*-Bu signals) in $CDCl_3$ at rt; (b) in DMSO-d_6 at rt. Only **12n** is observed, and no signals are at <10 ppm. (c) ^{13}C NMR spectrum in $CDCl_3$ at rt.

signals with similar intensities. For **12** the C=S and C=O signals are at 183.16–187.67 ppm and 158.78–162.37 ppm, respectively; for **11** the C=S and C_α(E) are at 184.75–189.88 ppm and 170.41–173.26 ppm, respectively. Mostly, δ(C=S, **11**) > δ(C=S, **12**). The C=O and C_α signals of **13** are at 164.80–169.38 ppm (**13k** at 173.26 ppm). The C≡N signals are doublets (J = 9.5–11.0 Hz) at 113.85–114.64 ppm for **12** and at 117.93–120.04 ppm for **11**, and are singlets at 120.21–121.78 ppm for **13**. The coupled C_β signals are doublets at 50.15–58.65 ppm (J = 139.2–143.2 Hz) for **12**, and the C_β signals are singlets for **11** and **13** at 65.93–68.09 and 69.82–73.04 ppm, respectively.

Substituent and solvent effects

The substituents R^1–R^3 have an effect on the distribution of the three species, and the derived K_{enol} for $R^1R^2NCOCH(CN)CSNHR^3$ in different solvents at rt is given in Table 4.

For NMe_2 systems the %(**12**) in $CDCl_3$ is much higher for the aliphatic R^3 = Alk, when **13** is not observed, than when R^3 = Ph, *p*-An, 1-Np, where **13** is present in 16–29%. When R^3 = Ph, *p*-An, %(**11**) > %(**13**), whereas the %(**11** + **13**) is higher when R^3 = 1-Np, but the %(**13**) slightly exceeds the %(**11**). A similar trend was observed for other NR^1R^2 systems (Table 4). The effects of R^1–R^3 on the % and the *K*'s of the various species are shown in Table 4. The %(**11** + **13**) increases by successively replacing the Me groups in NR^1R^2 by hydrogens, as was observed for the **7/8/9** system and in calculations.[8] Thus, for R^3 = Alk, the %(**12**) is 88–96%, 22–37% and 7–24% for NR^1R^2 = NMe_2, NHMe and NH_2, respectively, and a similar trend was found for R^3 = Ar. Systematically, K_{enol} > $K_{thioenol}$ for R^3 = Alk, Ph. In both $CDCl_3$ and THF-d_8, **12** is the major species for the NMe_2 derivative, a minor component for NHMe and is absent for the NH_2 derivative. For the NHMe and NH_2 derivatives **11h/12h/13h** and **11o/12o/13o**, the %(**13**)/%(**11**) in $CDCl_3$ is *ca.* 1.1 and 1.5, respectively. However, in THF-d_8 $K_{enol}/K_{thioenol}$ = 11 for NHMe, and 49 for NH_2 when R^3 = Ph. For **11h–n/12h–n/13h–n**, the %(**11**) decreased on increasing the bulk of R^3: Me (71) > Et (68) ≈ i-Pr (66) > *t*-Bu (45) ≈ Ph (46) > *p*-An (43) > 1-Np (31). The %(**12**) and %(**13**) increase on increasing the steric effect according to *t*-Bu > i-Pr ≈ Et > Me (Table 4).

The percentage of enolization and thioenolization decreases on increasing the solvent polarity from CCl_4 to DMSO-d_6 (Table 4), as found earlier for enols of amides.[3,4,8] In the highly polar DMSO-d_6 and DMF-d_7, and also for several systems in CD_3CN, only **12** is observed. The highest %(**13**) for all systems is in $CDCl_3$. In $CDCl_3$ and CCl_4, $K_{thioenol}$ resembles or is higher than K_{enol} for aromatic R's. In the other solvents K_{enol} > $K_{thioenol}$.

Discussion

Comparison of the solid state structures of 6/7/8 and 11/12/13

The X-ray solid state structures of three analogous pairs of the two series can be compared: (i) i-PrNH(C=Z)CH(CN)$CONMe_2$ (**I**), in which Z = O, S have amide structures with small bond length differences (Δ_{OS} = 0.003–0.0096 Å) between Z = O and Z = S. For **I** in $CDCl_3$, Z = O is 80% enol and Z = S is 12% enol; (ii) PhNH(C=Z)CH(CN)CONHMe (**II**), in which Z = O displays an amide structure, whereas for Z=S it crystallized as an enol, although in $CDCl_3$ the %(enol) is 90% (Z = O) and 46% (Z = S); (iii) *p*-AnNH(C=Z)CH(CN)CONHMe (**III**), in which Z = O, S are both enols, with small bond length differences (Δ_{OS} = 0.004–0.03 Å). The C(1)–C(2) bond lengths of 1.401 Å for Z = O and 1.422 Å for Z = S indicate a lower single bond character for the

Table 3 Selected ^{1}H NMR δ values (in ppm) for **11/12/13** systems in several solvents at room temperature

Compound	R^3	Solvent	δ(OH) (E, **11**)	δ(CH) (TMA, **12**)	δ(SH) (TE, **13**)
11a/12a/13a	Ph	$CDCl_3$	16.64	5.33	4.58
11b/12b/13b	*p*-An	$CDCl_3$	16.61	5.33	4.53
11c/12c/13c	1-Np	CCl_4	16.56	5.01	4.29
		$CDCl_3$	16.64	5.49	4.50
		C_6D_6	17.29	5.09	4.27
		THF-d_8	16.89	5.79	5.17
		CD_3CN	16.52	5.65	5.11
11h/12h/13h	Ph	$CDCl_3$	16.85	5.05	4.45
		THF-d_8	17.09	5.03	6.89
		CD_3CN	16.85	5.05	6.80
11i/12i/13i	*p*-An	$CDCl_3$	16.85	4.94	4.36
		THF-d_8	17.12	5.01	4.85
		CD_3CN	16.86	5.01	4.55
11j/12j/13j	1-Np	$CDCl_3$	16.83	[a]	4.34
		THF-d_8	17.11	5.30	6.97
		CD_3CN	16.79	5.36	6.34
11k/12k/13k	Me	$CDCl_3$	16.59	4.88	4.55
11l/12l/13l	Et	$CDCl_3$	16.64	4.87	4.54
11m/12m/13m	i-Pr	$CDCl_3$	16.68	4.85	5.84
11n/12n/13n	*t*-Bu	CCl_4	16.57	4.21	4.47
		$CDCl_3$	16.88	4.79	4.79
		C_6D_6	17.43	4.09	5.44
11o/12o/13o	Ph	$CDCl_3$	16.61	[a]	4.47
11r/12r/13r	i-Pr	$CDCl_3$	16.46	4.68	5.22
11s/12s/13s	*t*-Bu	$CDCl_3$	16.66	4.75	4.88
		C_6D_6	17.02	4.29	3.87
11t/12t/13t	Ph	$CDCl_3$	16.82	5.17	4.70
		THF-d_8	17.11	5.04	6.35
11u/12u/13u	i-Pr	$CDCl_3$	16.64	4.83	5.26
11v/12v/13v	i-Pr	$CDCl_3$	16.94	4.81	4.63
11w/12w/13w	*t*-Bu	$CDCl_3$	17.09	4.79	4.83
11x/12x/13x	*t*-Bu	$CDCl_3$	17.31	4.86	4.90

[a] The CH or other signals of the TMA were not observed.

latter. For **III** in $CDCl_3$, Z = O is 90% enol, and Z = S is 43% enol. We conclude that there is no correlation between the %(enol) in solution and the structure of the crystallized species. The data are reported in Table S4 in the ESI.§

Enolization on C=O *vs.* thioenolization on C=S

A main theme of this work is the intramolecular competition between enolization on C=O and thioenolization on C=S. Both processes have been previously compared in terms of both intermolecular and intramolecular competition as shown below. For single enolization sites thioenolization is qualitatively much more facile than enolization. Simple thioenols are observable species[13] but the corresponding enols are usually unobservable.[6] Recent measurements illustrate this point: $K_{thioenol}/K_{enol} = \geq 10^6$, *ca.* 10^4, 10^6 and 10^5 when X = S, O for $Ph_2CHC(=X)Ph$,[14] 9-C(=X)OMe-fluorenes,[15] mesityl-C(=X)Me[16a] and benzo[*b*]-2,3-dihydrothiophene-2-(=X).[16b]

The higher extent of thioenolization is ascribed[17] to the much weaker C=S bond than the C=O bond (115 *vs.* 177 kcal mol^{-1}),[18] which is not compensated by the smaller C–S and S–H bond energies than those of C–O and O–H bonds (61, 82, 88 and 110 kcal mol^{-1}).[18] From these values thioenolization is 7 kcal mol^{-1} more favored than the enolization, as reflected in the experimental values. However, these O–H and S–H bond energies are for saturated systems, and for triarylethenols the O–H BDE is *ca.* 80 kcal mol^{-1}.[19] Extensive calculations[17] for the $CH_3CH{=}X$ systems (X = S, O) show that thioenolization ($\Delta H = -5.5$–8 kcal mol^{-1}) is always favored over enolization ($\Delta H = 5$–17 kcal mol^{-1}). For $(CH_3)_2C{=}X$, the $\Delta(\Delta H)$ value is 8.8 kcal mol^{-1} at B3LYP/6–31G**. In less extensive calculations $\Delta(\Delta H) = 8$–11 kcal mol^{-1}.[20]

These large differences do not apply for *intramolecular* competitive enolization in an O=C–CH–C=S system. Our systems are the first where such competition involves C=O and C=S sites of amides and thioamides. A competitive *intermolecular* enolization on esters strongly favors the C=S site.[15,21] However, for 1,3-thioxoketones R′C(=O)CHRC(=S)R″ (R′, R″ = Alk, Ar),[22] the situation is more complex. The many techniques used to determine whether enolization or thioenolization is preferred gave different answers.[22] Complications arise from the simultaneous presence of thioxoketone, *cis* (with an O–H $\cdots$ S=C hydrogen bond) and *trans* enols, and *cis* (with a S–H $\cdots$ O=C hydrogen bond) and *trans* thioenols. The observation of only one NMR (OH/SH) signal at rt is ascribed to a rapid prototropic equilibrium between few species, especially the *cis* enol and thioenol, which average the NMR signals. Indeed, in a low temperature dynamic NMR study[22h] both species plus a minor percentage of the non-hydrogen bonded *Z*-thioenol were observed. The large intermolecular preference of enolization over thioenolization had disappeared, presumably due to a counter-effect of intramolecular O–H $\cdots$ S and

Table 4 Effect of R^1, R^2, R^3 and the solvent on K_{enol}, $K_{thioenol}$ and K_{total} for **11/12/13** systems[a]

Compound	R^3	Solvent	% **12**	% **11**	% **13**	K_{total}	K_{enol}	$K_{thioenol}$
11a/12a/13a	Ph	$CDCl_3$	60	24	16	0.67	0.40	0.27
		THF-d_8	91	9	0	0.10	0.10	0
		CD_3CN	96	4	0	0.04	0.04	0
11b/12b/13b	*p*-An	$CDCl_3$	61	23	16	0.63	0.38	0.25
		THF-d_8	94	6	0	0.06	0.06	0
		CD_3CN	97	3	0	0.03	0.03	0
11c/12c/13c[b]	1-Np	CCl_4	33	35	32	2.03	1.06	0.97
		$CDCl_3$	44	27	29	1.27	0.61	0.66
		C_6D_6	58	28	14	0.72	0.48	0.24
		THF-d_8	86	12	2	0.16	0.14	0.02
		$(CD_3)_2CO$	92	7	1	0.09	0.08	0.01
		CD_3CN	94	5	1	0.06	0.05	0.01
11d/12d/13d[c]	Me	$CDCl_3$	88	12	0	0.14	0.14	0
		THF-d_8	96	4	0	0.05	0.05	0
11e/12e/13e[c]	Et	$CDCl_3$	92	8	0	0.09	0.09	0
		THF-d_8	96	4	0	0.05	0.05	0
11f/12f/13f[c]	i-Pr	CCl_4	72	28	0	0.039	0.39	0
		$CDCl_3$	88	12	0	0.14	0.14	0
		THF-d_8	97	3	0	0.03	0.03	0
11g/12g/13g[c]	*t*-Bu	CCl_4	89	11	0	0.13	0.13	0
		$CDCl_3$	96	4	0	0.04	0.04	0
		THF-d_8	100	0	0	$\leq$0.02	$\leq$0.02	$\leq$0.02
11h/12h/13h	Ph	$CDCl_3$	4	46	50	24.00	11.50	12.50
		THF-d_8	19	74	7	4.17	3.81	0.36
		CD_3CN	38	54	8	1.66	1.45	0.21
11i/12i/13i	*p*-An	$CDCl_3$	4	43	53	25.89	11.73	14.16
		THF-d_8	20	75	5	4.07	3.8	0.27
		CD_3CN	39	53	8	1.58	1.37	0.21
11j/12j/13j	1-Np	$CDCl_3$	0	31	69	$\geq$50		
		THF-d_8	15	76	9	5.66	5.04	0.62
		$(CD_3)_2CO$	29	65	6	2.43	2.23	0.20
		CD_3CN	33	55	12	2.08	1.70	0.38
11k/12k/13k	Me	$CDCl_3$	22	71	7	3.54	3.23	0.31
		THF-d_8	34	66	0	1.97	1.97	0
		CD_3CN	67	33	0	0.50	0.50	0
11l/12l/13l	Et	$CDCl_3$	22	68	10	3.64	3.14	0.50
		THF-d_8	38	62	0	1.62	1.62	0
		CD_3CN	70	30	0	0.44	0.44	0
11m/12m/13m	i-Pr	$CDCl_3$	23	66	11	3.35	2.87	0.48
		THF-d_8	47	53	0	1.13	1.13	0
		CD_3CN	77	23	0	0.30	0.30	0
11n/12n/13n[b]	*t*-Bu	CCl_4	14	74	12	6.19	5.32	0.87
		C_6D_6	31	62	7	2.23	2.02	0.21
		$CDCl_3$	37	45	18	1.64	1.18	0.46
		THF-d_8	66	34	0	0.51	0.51	0
		CD_3CN	89	11	0	0.12	0.12	0
11o/12o/13o	Ph	$CDCl_3$	0	40	60	$\geq$50		
		THF-d_8	0	98	2	$\geq$50		
11p/12p/13p	*p*-An	$CDCl_3$	0	39	61	$\geq$50		
11q/12q/13q	1-Np	THF-d_8	0	100	0	$\geq$50		
11r/12r/13r	i-Pr	$CDCl_3$	24	66	10	3.17	2.75	0.42
11s/12s/13s[b]	*t*-Bu	C_6D_6	0	90	10	$\geq$50		
		$CDCl_3$	7	70	23	14.12	10.6	3.53
		THF-d_8	17	83	0	5.01	5.01	0
		CD_3CN	67	33	0	0.49	0.49	0
11t/12t/13t	Ph	$CDCl_3$	54	9	37	0.86	0.16	0.69
		THF-d_8	31	64	5	2.23	2.06	0.17
		CD_3CN	49	45	6	1.04	0.92	0.12
11u/12u/13u	i-Pr	$CDCl_3$	23	70	7	3.47	3.15	0.32
		THF-d_8	61	39	0	0.64	0.64	0
		CD_3CN	85	15	0	0.18	0.18	0
11v/12v/13v[c]	i-Pr	$CDCl_3$	11	65	24	8.45	6.16	2.29
		THF-d_8	80	20	0	0.25	0.25	0
11w/12w/13w[c]	*t*-Bu	$CDCl_3$	31	42	27	2.21	1.35	0.86
		THF-d_8	90	10	0	0.11	0.11	0
11x/12x/13x[c]	*t*-Bu	$CDCl_3$	20	32	48	4.15	1.69	2.46
		THF-d_8	17	83	0	5.01	5.01	0

[a] For all systems only **12** was observed in DMSO-d_6. [b] Only **12** was observed in DMF-d_7. [c] Only **12** was observed in CD_3CN.

O · · · H–S hydrogen bonds of different strengths, whose magnitudes were disputed.[23]

β-Oxothioacetamides, which were also investigated by NMR, are written as the enols R′C(OH)=CRC(=S)NR′R‴, displaying only one (presumably OH) signal at δ 14.2–15.2.[24]

Structures of enols 11 and thioenols 13 in solution

Potential enol and thioenol structures (Chart 1 and 2) are the *Z-syn* thioenol **14** with an S–H · · · O=C bond and a *Z-syn* enol **18** with an O–H · · · S=C hydrogen bond. In both the two double bonds are in an *s-syn* arrangement. These 6-membered ring structures are analogous to the most stable structures for the cyanomalonamides **7**/**8**[8] where the NR^1R^2 and NHR moieties are not involved in hydrogen bonding. Rotation around the C–C(=X) bond (X = O, S) gives the *Z-anti* structures with an S–H · · · NR^1R^2 hydrogen bond for **15** or an O–H · · · NHR^3 bond for **19**. Formal rotation around the C=C bond generates the *E*-isomers. In the *E-syn* enol, if the *cis*-NR^1R^2 to the C=S contains no hydrogen there is no hydrogen bond, but if R^1 and/or R^2 = H, an N–H · · · S=C hydrogen bond exists in **20**. Since in all the cyanomonothiocarbonylmalonamides the thioamide nitrogen carries one hydrogen, there is an N–H · · · O=C hydrogen bond in the *E-syn* thioenol **16**. An N–H · · · N bond exists in both the *E-anti* enol and thioenol isomers (**17** and **21**) and if R^1 and/or R^2 = H, there are several options for such a bond. Consequently, the combination of dipole–dipole attraction and repulsion interactions, and different hydrogen bonds in the various structures, make it difficult to unequivocally determine the structure in solution. The solid state structure is not necessarily identical to that in solution and analogy with **7**/**8** is useless since the C=O → C=S change affects the nature of the hydrogen bond. In **12** there are intramolecular N–H · · · O=C bonds if one of the R groups = H.

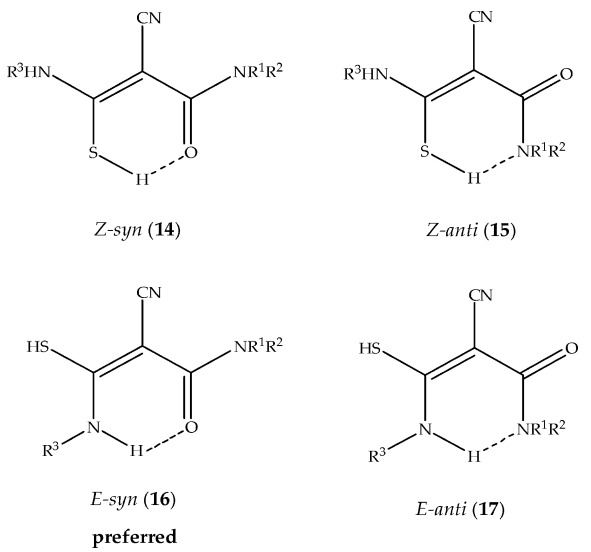

Chart 1 Possible structures for the thioenols of cyanomonothiocarbonylmalonamides.

In our systems the nitrogen adjacent to the C=S is connected to one hydrogen and only in the *E-syn* enols is there no C=S · · · H–N bond when R^1, $R^2 \neq$ H. In analysing the relative stabilities

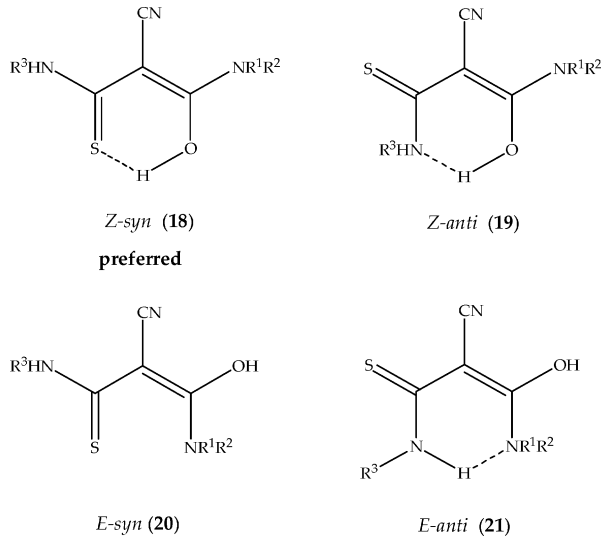

Chart 2 Possible structures for the enols of cyanomonothiocarbonylmalonamides.

of the various configurations/conformations of **14**–**21** arising from the contribution of the hydrogen bonds, we assume that the C=S · · · H–N and the S–H · · · N hydrogen bonds are weaker than the C=O · · · H–N and O–H · · · N bonds.

A valuable probe is the difference in the two δ(N–H) values for each species when R^1 or R^2 = H. We expect a large difference when only one, low field hydrogen participates in a hydrogen bond and a relatively small difference when both N–H bonds do not form hydrogen bonds. Analysis shows that the N–H bond is involved in hydrogen bonding for the *E-anti* enol and thioenol and for the *E-syn* thioenols. If R^1 = H, a large value is also predicted for the *E-syn* enol.

When $R^1 = R^2$ = Me each species displays only one NH signal: at δ 12.14–13.19 for **13**, at δ 10.45–11.13 (R^3 = Ar) and 8.65–9.00 (R^3 = Alk) for **12**, and at δ = 8.33–8.49 (R^3 = Ar) and 6.81–7.26 (R^3 = Alk) for **11** (Table 5). When R^1 = H, R^2 = Me, the order of δ values is retained, but each species display two signals. The $\Delta\delta$(N–H) values of 4.20–7.08 for **13** > $\Delta\delta$ 2.97–3.52 (R^3 = Ar) and 1.69–2.50 (R^3 = Alk) for **12** > $\Delta\delta$ 1.59–2.17 (R^3 = Ar) and 0.27–1.16 (R^3 = Alk) for **11** (Table 5). For $R^1 = R^2$ = H, $\Delta\delta$ = 6.19–7.21 for **13**, 2.50 for **12** and 1.13–2.76 for **11**.

Consequently, the large $\Delta\delta$ values for **13** indicate an *E*-configuration (**16** or **17**) and the significantly lower $\Delta\delta$ values for **11** indicate a *Z* configuration (**18** or **19**). This conclusion is consistent with the δ(OH) of >16.5 ppm (Table 3) observed for other hydrogen bonded enols,[3,4,8] and hence **18** is the preferred conformation for the enol; *e.g.*, for enols ArNHC(OH)=C(CN)CO_2R (R=CF_3CH_2 and $(CF_3)_2CH$),[4c] δ(OH) for the *Z*-isomers is mostly at δ 13.2–14.5, and moves 2–3 ppm to a higher field for the *E*-isomers. The NH values are at *ca.* δ 8.3–10.0 for the *Z*-enols and at δ 10.2–10.9 for the *E*-enols.

The low field δ(SH) signals at 4.3–4.8 in $CDCl_3$ (Table 3) are consistent with a non-hydrogen bonded SH group in the *E*-thioenols. Since an N–H · · · O is a stronger hydrogen bond than an N–H · · · N bond, the structure should be *E*-syn **16**. The δ of 6.3–6.9 for the NHMe derivatives in CD_3CN and THF-d_8 is

Table 5 δ(NH) values and their differences $\Delta\delta$ (in ppm) for each of the **11/12/13** systems in several solvents at room temperature

			Enol **11**			Amide–thioamide **12**			Thioenol **13**		
Compound	R^3	Solvent	NHR^3/ppm	NR^1R^2/ppm	$\Delta\delta$/ppm	NHR^3/ppm	NR^1R^2/ppm	$\Delta\delta$/ppm	NHR^3/ppm	NR^1R^2/ppm	$\Delta\delta$/ppm
11a/12a/13a	Ph	$CDCl_3$	8.49	—	—	10.60	—	—	12.40	—	—
11b/12b/13b	*p*-An	$CDCl_3$	8.43	—	—	10.51	—	—	12.14	—	—
11c/12c/13c	1-Np	CCl_4	8.33	—	—	10.45	—	—	12.77	—	—
		$CDCl_3$	8.71	—	—	11.13	—	—	12.72	—	—
		C_6D_6	8.86	—	—	11.13	—	—	13.19	—	—
11d/12d/13d	Me	$CDCl_3$	7.26	—	—	9.00	—	—	—	—	—
11e/12e/13e	Et	$CDCl_3$	7.00	—	—	8.73	—	—	—	—	—
11f/12f/13f	i-Pr	$CDCl_3$	6.81	—	—	8.65	—	—	—	—	—
11g/12g/13g	*t*-Bu	$CDCl_3$	6.97	—	—	8.67	—	—	—	—	—
11h/12h/13h	Ph	$CDCl_3$	8.21	6.32	1.89	10.90	7.75	3.15	12.80	5.97	6.83
		THF-d_8	9.20	7.60	1.60	11.29	7.84	3.36	13.19	6.87	6.32
		CD_3CN	8.61	6.80	1.81	10.53	7.01	3.52	12.80	6.30	6.50
11i/12i/13i	*p*-An	$CDCl_3$	8.10	6.08	2.02	10.54	7.61	2.93	12.52	5.88	6.64
		THF-d_8	9.11	7.52	1.59	11.15	7.82	3.33	12.88	6.83	6.05
		CD_3CN	8.51	6.73	1.78	10.38	6.96	3.42	12.59	6.23	6.36
11j/12j/13j	1-Np	$CDCl_3$	8.37	6.20	2.17	—	—	—	13.05	5.97	7.08
		THF-d_8	9.53	7.66	1.87	11.55	8.07	3.48	13.51	6.98	6.53
		CD_3CN	8.84	6.83	2.01	10.92	7.43	3.49	13.12	[a]	[a]
11k/12k/13k	Me	$CDCl_3$	6.90	6.13	0.77	9.17	7.06	2.11	11.02	5.82	4.20
		C_6D_6	6.40	5.24	1.16	8.35	5.78	2.57	11.04	5.51	5.53
11l/12l/13l	Et	$CDCl_3$	6.70	6.18	0.52	9.07	7.10	1.97	11.07	5.85	5.22
11m/12m/13m	i-Pr	$CDCl_3$	6.44	6.17	0.27	8.91	7.05	1.86	11.14	5.84	5.30
11n/12n/13n	*t*-Bu	$CDCl_3$	6.55	6.05	0.5	8.74	7.05	1.69	11.61	5.81	5.80
11o/12o/13o	Ph	$CDCl_3$	8.31	5.55	2.76	—	—	—	12.70	5.49	7.21
11s/12s/13s	*t*-Bu	$CDCl_3$	6.73	5.60	1.13	8.36	5.86	2.50	11.58	5.93	6.19

[a] Signal not observed.

consistent with intermolecular hydrogen bonds of the SH with the hydrogen bond accepting solvents. Indeed, in β-thioxoesters $HSC(R^1)=CHCO_2R^2$ the intramolecular S–H···O=C hydrogen bonded *Z*-isomer displays δ(SH) at 5.68–8.19 ppm, which is at *ca.* δ 3.80 for the *E*-isomer.[22a] A structure related to **20** with a "free" SH group was detected earlier in solution.[22h,l]

Comparison of δ(OH) and K_{enol} values of the enols 11 and 7/8

A qualitative comparison between the **11/12/13** and **6/7/8** systems show, in $CDCl_3$, a 0.69–1.69 ppm lower field δ(OH) in the latter, ascribed to a better O–H···O=C than an O–H···S=C hydrogen bond. K_{enol} and K_{total} values are significantly higher for **6/7/8**. The ratios for PhNH(C=Z)CH(CN)CONRMe (Z = O, S) are >10-fold higher for R = Me than for R = H (4.01–4.5 for R^3 = Alk and 0.77–0.78 for R^3 = Ar). For i-PrNH(C=Z)CH(CN)CONHPr-i the ratio is 2.57. Hence, the extent of enolization is strongly structure-dependent. The corresponding data are reported in Table S5 in the ESI.§

Solvent and substituent effects on K_{enol} and $K_{thioenol}$

K_{enol} and $K_{thioenol}$ are strongly solvent- and substituent-dependent (Table 4). K_{enol} values increase on decreasing the solvent polarity, following the order CCl_4 > $CDCl_3$ > C_6D_6 > THF-d_8 > $(CD_3)_2CO$ > CD_3CN > DMF-d_7 > DMSO-d_6. The same trend was observed for $K_{thioenol}$, except that $CDCl_3$ > CCl_4. In contrast with compounds **6/7/8**, where the NHMe and NH_2 derivatives display the enol in DMSO-d_6,[8] for compounds **11/12/13**, **12** is the exclusive tautomer in DMSO-d_6.

For a constant NHR^3, both K_{enol} and $K_{thioenol}$ decrease for NR^1R^2 in the order NH_2 > NHMe > NMe_2. Thus, for **11h–j/12h–j/13h–j** and **11o–p/12o–p/13o–p**, **13** predominates in $CDCl_3$, and **12** predominates for **11a–g/12a–g/13a–g** systems. Moreover, for NMe_2 systems no **13** was observed for R^3 = Alk and a small to moderate %(**13**) was observed when R^3 = Ar. The %(**13**) for NHMe and NH_2 systems was independent of R^3.

Conclusions

Replacing one C=O with a C=S group in $R^3NHCOCH(CN)$-$CONR^1R^2$ leads to seven changes: (i) both enolization and thioenolization are observed in solution. (ii) The intramolecular O–H···O hydrogen bonded *Z*-enol structures in the **6/8** and **11/13** systems are analogous, whereas the thioenol structure has the *E*-configuration, no intramolecular H-bonded SH group and an intramolecularly N–H···O H-bonded moiety. (iii) δ(OH) values in **7** are at a lower field than in analogs **11**. (iv) K_{enol} values for **11/12/13** are lower than in **6/7/8**. (v) The thioenol **13** is less stable than enol **11** for S=C-*N*-Alk-substituted systems, but the stabilities are much closer and even slightly reversed for *N*-aryl systems. An increased number of N–H bonds adjacent to the C=O strongly increases the $K_{thioenol}$ and K_{enol} values. (vi) Compounds **11/12/13** are more reactive, giving an array of different reactions.[11] (vii) The intramolecular hydrogen bond strengths are important in determining the structures of the enols and thioenols and the differences between them.

Experimental section

General methods, NMR and analytical data

Melting points, ^{1}H and ^{13}C NMR and IR spectra were measured as described previously.[2f] All the commercial precursors and solvents were purchased from Aldrich.

δ values are relative to Me_4Si. *J* values are given in Hz. Analytical data, mps and yields are given in Table S6 in the ESI.§

Reaction of *N*,*N*-dimethylcyanoacetamide with phenyl, *p*-anisyl, 1-naphthyl, methyl, ethyl, isopropyl and *tert*-butyl isothiocyanates to form 11a–g/12a–g/13a–g

The procedure for isopropyl isothiocyanate was also used with the other isothiocyanates.

To a suspension of Na (0.25 g, 11 mmol) in dry THF (50 mL) was added *N*,*N*-dimethylcyanoacetamide (1.12 g, 10 mmol) and the mixture was stirred overnight giving a white precipitate. A solution of isopropyl isothiocyanate (1.08 mL, 10 mmol) in dry THF (20 mL) was added dropwise to the stirred mixture over 20 min. After stirring overnight at rt the dissolved white precipitate gave a yellow solution. The solvent was evaporated, the remaining Na salt was dissolved in DMF (5 mL) and the solution was added slowly to a cold 2 N HCl solution (100 mL). The formed yellowish precipitate was filtered, washed with cold water (30 mL) and dried in air to give 1.96 g (92%) of **12f**, mp 147–9 °C. Anal. calcd for $C_9H_{15}N_3OS$: C, 50.70; H, 7.04; N, 19.72; found: C, 50.30; H, 7.06; N, 19.42%. Crystals for X-ray diffraction were obtained by keeping a solution of **12f** in THF-d_8 or $CDCl_3$ at rt for 2–3 weeks. Detailed NMR spectra of **11f/12f** and the analogous preparation and spectra of **11c** are given in the ESI.§ Spectral data, mps, yields and analyses are given in Tables 3, S1–S3 and S6.

Reaction of *N*-methylcyanoacetamide with phenyl, *p*-anisyl, 1-naphthyl, methyl, ethyl, isopropyl and *tert*-butyl isothiocyanates to form 11h–n/12h–n/13h–n

The procedure is demonstrated for phenyl isothiocyanate. Very small Na pieces (0.25 g, 11 mmol) were added to an *N*-methylcyanoacetamide (0.98 g, 10 mmol) solution in dry THF (50 mL) under nitrogen. The mixture was stirred for 48 h until complete Na disappearance, giving a white precipitate in an orange solution. A solution of phenyl isothiocyanate (1.2 mL, 10 mmol) in dry THF (20 mL) was added dropwise over 30 min and during 6 h reflux the precipitate dissolved to give a dark orange solution. Removal of the solvent left the brown salt $[PhNHCSC(CN)CONHMe]^-Na^+$. δ_H (400 MHz, 298 K, DMSO-d_6): 2.61 (3H, d, *J* = 4.5, NMe), 6.94 (1H, t, *J* = 7.8, *p*-H), 7.21 (2H, t, *J* = 7.8, *m*-H), 7.79 (2H, d, *J* = 7.2, *o*-H), 13.20 (1H, s, NH). δ_C (100.133 MHz, 298 K, DMSO-d_6): 26.43 (q, *J* = 136.7, Me), 76.76 (s, C[anion]), 122.18 (d, *J* = 160.4), 122.75 (d, *J* = 162.4), 125.56 (s, CN), 128.32 (d, *J* = 161.1), 142.26 (s), 169.66 (s, C=O), 185.96 (s, C=S).

The salt was dissolved in DMF (5 mL) and the orange solution was added dropwise to a cold 2 N HCl solution (100 mL). The yellow precipitate was filtered, washed with cold water (200 mL) and dried in air to give 1.87 g (80%) of **11h**, mp 153–5 °C. Anal. calcd for $C_{11}H_{11}N_3OS$: C, 56.65; H, 4.72; N, 18.03; found: C, 56.72;

H, 4.86; N, 17.79%. Crystals for X-ray diffraction were obtained by slow evaporation of the EtOAc solution at rt.

Attempts to obtain the 1-naphthyl derivative, **11j**, gave a product in 89% yield, mp 158–60 °C. However, crystallization from EtOAc at rt gave a 5-membered ring compound resulting from an oxidation reaction, apparently by air oxygen.[11] Crystallization from EtOAc under nitrogen revealed the enol structure **11j**. Compounds **11i**, **11l–n** were obtained similarly. The reaction of **11n** and the spectra of the **11n/12n/13n** obtained, and spectral and analytical data of all the compounds are given in Tables 3, S1–S3 and S6.

Reaction of cyanoacetamide with phenyl, *p*-anisyl, 1-naphthyl, isopropyl and *tert*-butyl isocyanates to form 11o–s/12o–s/13o–s

The procedure for all the derivatives is similar. To a heated solution of cyanoacetamide (0.84 g, 10 mmol) in dry THF (100 mL) at 60 °C was added Na (0.25 g, 11 mmol) and the mixture was stirred at 60 °C for 4 days, giving a white precipitate. The organic isothiocyanate (10 mmol) in dry THF (30 mL) was added dropwise during 30 min at rt. The mixture was refluxed for 48 h and then stood at rt for 1 h to give a brown solution and a white precipitate which was filtered and washed with dry ether giving the salt $[R^3NHCSC(CN)CONH_2]^-Na^+$. The salt solution in DMF (5 mL) was added dropwise to a cold 2 N HCl solution (100 mL), the solid obtained was filtered, washed with cold water (500 mL) and dried in air or in vacuum to give the pure product. Attempts to crystallize the products gave different heterocycles.[11] Their spectral and analytical data are given in Tables 3, S1–S3 and S6.

Reaction of *N*-isopropylcyanoacetamide with phenyl and isopropyl isothiocyanates to form 11t and 11u

The procedure resembles that of the reaction of *N*-methylcyanoacetamide with phenyl isothiocyanate. **11t**, mp 128–30 °C, was prepared from *N*-isopropyl cyanoacetamide (1.26 g, 10 mmol) and phenyl isothiocyanate (1.2 mL, 10 mmol) in 80% yield. **11u**, mp 157–8 °C, was prepared from *N*-isopropyl cyanoacetamide (1.26 g, 10 mmol) and isopropyl isothiocyanate (1.07 mL, 10 mmol) in 74% yield. The spectral and analytical data are in Tables 3, S1–S3 and S6

Reaction of *N*-benzhydrylcyanoacetamide with isopropyl and *t*-butyl isothiocyanates to form 12v and 12w

The procedure resembles the reaction of *N*,*N*-dimethylcyanoacetamide with isopropyl isothiocyanate. The isopropyl derivative **11v** (0.78 g, 89%), mp 162–4 °C, was obtained by reacting *N*-benzhydrylcyanoacetamide (0.625 g, 2.5 mmol) with isopropyl isothiocyanate (0.27 mL, 2.5 mmol). Crystals of **12v** for X-ray diffraction were obtained after long-term standing in $CDCl_3$. The *t*-butyl derivative **12w** (0.67 g, 73%), mp 166–8 °C, was obtained from *N*-benzhydrylcyanoacetamide (0.625 g, 2.5 mmol) and *t*-butyl isothiocyanate (0.29 mL, 2.5 mmol). The spectral and analytical data are in Tables 3, S1–S3 and S6.

Reaction of *N*-phenylcyanoacetamide with *t*-butyl isothiocyanate

The procedure resembles the reaction of *N*-methylcyanoacetamide with *t*-butyl isothiocyanate. *N*-Phenylcyanoacetamide (0.8 g, 5 mmol) reacted with *t*-butyl isothiocyanate (0.58 mL, 5 mmol) to yield 1.29 (87%) of **11x**, mp 147–8 °C (dec.). The spectral and analytical data are in Tables 3, S1–S3 and S6.

Crystal data

12d: $C_{21}H_{33}N_9O_3S_3$, $M = 555.74$, monoclinic, $a = 14.6537(11)$ Å, $b = 14.1922(11)$ Å, $c = 14.9966(12)$ Å, $\alpha = 90°$, $\beta = 108.8310(10)°$, $\gamma = 90°$, $U = 2951.9(4)$ Å^3, $T = 295(1)$ K, space group $P2(1)/c$, $Z = 4$, 29 673 reflections collected, 5779 independent reflections [R(int) = 0.0635]. The final wR(F2) = 0.1972 [$I > 2\sigma(I)$]. **12f**: $C_9H_{15}N_3OS$, $M = 213.30$, monoclinic, $a = 7.3690(4)$ Å, $b = 15.9322(8)$ Å, $c = 10.1036(5)$ Å, $\alpha = 90°$, $\beta = 98.6260(10)°$, $\gamma = 90°$, $U = 1172.79(10)$ Å^3, $T = 295(1)$ K, space group $P2(1)/c$, $Z = 4$, 12 869 reflections collected, 2557 independent reflections [R(int) = 0.0210]. The final wR(F2) = 0.1003 [$I > 2\sigma(I)$]. **12v**: $C_{20}H_{21}N_3OS$, $M = 351.46$, monoclinic, $a = 12.321(2)$ Å, $b = 18.376(3)$ Å, $c = 9.3465(16)$ Å, $\alpha = 90°$, $\beta = 116.339(3)°$, $\gamma = 90°$, $U = 1896.5(6)$ Å^3, $T = 295(1)$ K, space group Cc, $Z = 4$, 10 385 reflections collected, 4082 independent reflections [R(int) = 0.1157]. The final wR(F2) = 0.0973 [$I > 2\sigma(I)$]. **11h**: $C_{11}H_{11}N_3OS$, $M = 233.29$, triclinic, $a = 9.4637(5)$ Å, $b = 9.9527(6)$ Å, $c = 13.2117(8)$ Å, $\alpha = 81.3100(10)°$, $\beta = 79.1780(10)°$, $\gamma = 68.9710(10)°$, $U = 1136.10(11)$ Å^3, $T = 295(1)$ K, space group P–1, $Z = 4$, 12 684 reflections collected, 4900 independent reflections [R(int) = 0.0172]. The final wR(F2) = 0.1267 [$I > 2\sigma(I)$]. **11i**: $C_{12}H_{13}N_3O_2S$, $M = 263.31$, monoclinic, $a = 10.5904(6)$ Å, $b = 26.0342(14)$ Å, $c = 9.6563(5)$ Å, $\alpha = 90°$, $\beta = 99.0470(10)°$, $\gamma = 90°$, $U = 2629.2(2)$ Å^3, $T = 295(1)$ K, space group $P2(1)/c$, $Z = 8$, 30 522 reflections collected, 6255 independent reflections [R(int) = 0.0845]. The final wR(F2) = 0.1344 [$I > 2\sigma(I)$]. **11j**: $C_{15}H_{13}N_3OS$, $M = 283.34$, monoclinic, $a = 4.9892(4)$ Å, $b = 19.2928(14)$ Å, $c = 14.7103(12)$ Å, $\alpha = 90°$, $\beta = 99.0450(10)°$, $\gamma = 90°$, $U = 1398.34(18)$ Å^3, $T = 295(1)$ K, space group $P2(1)/n$, 15 798 reflections collected, 3056 independent reflections [R(int) = 0.0569]. The final wR(F2) = 0.0865 [$I > 2\sigma(I)$]. **12r**: $C_{8.50}H_{14}N_3OS_{1.50}$, $M = 222.32$, orthorhombic, $a = 8.4053(5)$ Å, $b = 14.8272(9)$ Å, $c = 18.2296(11)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $U = 2271.9(2)$ Å^3, $T = 293(1)$ K, space group $P2(1)2(1)2(1)$, $Z = 8$, 26 066 reflections collected, 4961 independent reflections [R(int) = 0.0344]. The final wR(F2) = 0.0689 [$I > 2\sigma(I)$].

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