ORGANIC LETTERS

2006
Vol. 8, No. 26
5931−5934

The First Example of Isomeric Solid Amide and Its Enol

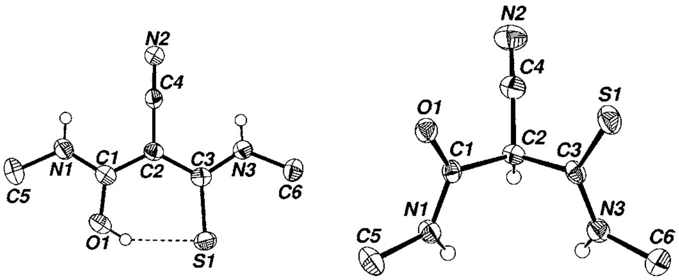
Ahmad Basheer and Zvi Rappoport*

Department of Organic Chemistry, The Hebrew University, Jerusalem 91904, Israel

zr@vms.huji.ac.il

Received September 21, 2006

ABSTRACT

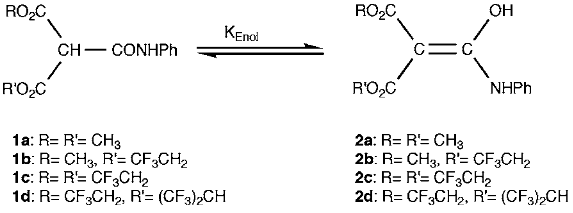


Enol   Amide

The first example of a crystalline amide and its tautomeric enol was obtained for the amide MeNHCSCH(CN)CONHMe (8) and its enol MeNHCSC(CN)=C(OH)NHMe (9). Their X-ray structures were determined, and their structural features resemble those of other related amides and enols. No other example of a similar pair was obtained. In solution, both 8 and 9 and a small percentage of the isomeric enol of thioamide MeNHCOC(CN)=C(SH)NHMe (10) were obtained in solvent-dependent compositions, which are rapidly established.

Carbonyl/enol isomeric equilibrium is one of the oldest topics studied in physical organic chemistry.[1] For "simple" systems (i.e., with H, alkyl, and non-bulky aryl substituents), the enol is usually much less stable than the carbonyl compound. There are two types of exceptions to this generalization. Monoenols of activated systems such as 1,3-dicarbonyl compounds are frequently more stable than the diketone, and the individual species were sometimes separated.[2] Several enols substituted by bulky aromatic substituents are stable in solution and in the solid state, and the two isomers of several isomeric pairs are known.[3,4] We determined by X-ray diffraction the structures of the enol trimesitylethenol ($Mes_2C{=}C(OH)Mes$, Mes = mesityl) and the carbonyl trimesitylethanone ($Mes_2CHCOMes$).[4]

Simple enols of carboxamides are much less stable than simple enols.[5] When activated by strongly electron-withdrawing groups capable of delocalizing a negative charge by resonance, the enols are stabilized. In solution, both the amide and its enol are observed in a mixture, and both types of species were isolated as solids and their structures were studied by X-ray diffraction. Usually, but not always, the isolated crystals from an equilibrium mixture of both species are of the more stable one in solution as deduced from the amide/enol equilibrium constant K_{Enol} = [Enol]/[Amide]. An example is the series



(1)

of diester-activated systems **1**/**2** (eq 1).[6] K_{Enol} value (e.g., in $CDCl_3$) increases with the number of fluorine atoms in R

---

(1) *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 1990.

(2) Toullec, J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 1990; Chapter 5, pp 330−331.

(3) Hart, H.; Rappoport, Z.; Biali. S. E. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 1990; Chapter 9.

(4) Kaftory, M.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 1701.

(5) If the compound is not highly activated, only the amide is observed. The enol of acetamide was calculated to be 28.8 kcal/mol less stable than acetamide at B3LYP/6-31G**//B3LYP/6-31G**: Sklenak, S.; Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* **1998**, *120*, 10359.

10.1021/ol062322z CCC: $33.50

and R′: **1a**, R = R′ = Me, 0.05;[6] **1b**, R = Me, R′ = CF_3CH_2, 0.35;[7] **1c**, R = R′ = CF_3CH_2, 6.70;[7] **1d**, R = CF_3CH_2, R′ = $(CF_3)_2CH$, ≥50.[7] The solid-state structures of the isolated species are **1a**, **1b**, **2c**, and **2d**.[6,7] However, there are several cases, such as *i*-PrNHCOCH$(CO_2Me)_2$ **3**, where the enol is the major species in CCl_4,[8] and 2-anilido-4,5-dimethylcyclopent-4-ene-1,3-dione **4**, where the enol predominates in $CDCl_3$,[9] but the amide is the isolated solid species for both systems.

So far, although we obtained ca. 25 enol of amide structures, we never obtained crystals of both the amide and its enol of *an isomeric pair*. This could have been possible since for many systems the solvent effect on the amide/enol of amide distribution (i.e., K_{Enol}) is strongly dependent on the solvent. For example, whereas **2c** and **2d** comprise 87 and 100%, respectively, of the enol/amide mixture in $CDCl_3$ solution, they are not observed in DMSO-d_6.[6]

We report here the first case where both the amide and its tautomeric enol were isolated in the solid state and their structures were determined. The reaction of *N*-methyl cyanoacetamide **5** with sodium in THF followed first by addition of methyl isothiocyanate **6** and then by protonation of the formed ambident ion **7** gave a mixture in which we identified three species in $CDCl_3$ solution: the amide thioamide **8**, the enol thioamide **9**, and the thioenol amide **10** (eq 2). The definitions of the corresponding equilibrium constants K_{Enol} and $K_{Thioenol}$ are given in Table 1. The formation of three species in analogous reactions of active methylene compounds with organic isothiocyanates was observed in >20 systems.[10] Here we will bring only relevant data to the specific systems **8**−**10**.

In contrast with other enols of amides, since **8** has a 1,3-thio and carbonyl moieties (i.e., thioamide and amide groups), two enolization processes, one on the C═O group giving **9** and one on the C═S group giving **10**, are possible, and both were observed in the low dielectric constant solvents. The composition of the solution was determined by the average relative integration of 15 ^1H NMR signals, all of which were conveniently well separated from one another: the singlets for the CH of **8**, the OH of **9**, the SH of **10**, the two broad NH signals and the doublets (J = 4.6−4.8 Hz) for the two Me signals for each species. In $\delta(CDCl_3)$, these signals appeared at 2.86, 3.17, 7.06 and 9.17, and 4.88 (CH) for CSN*Me*, CON*Me*, CSN*H*, and CON*H* of **8**, 2.96, 3.13, 6.13, 6.90, and 16.53 (OH) of **9**, and 2.80, 3.07, 11.02, 5.82, and 4.55 (SH) of **10**. The results based on either the Me, the NH, or the OH, SH, CH signals were very similar, and the average value was used for calculating the **8/9/10** ratios.

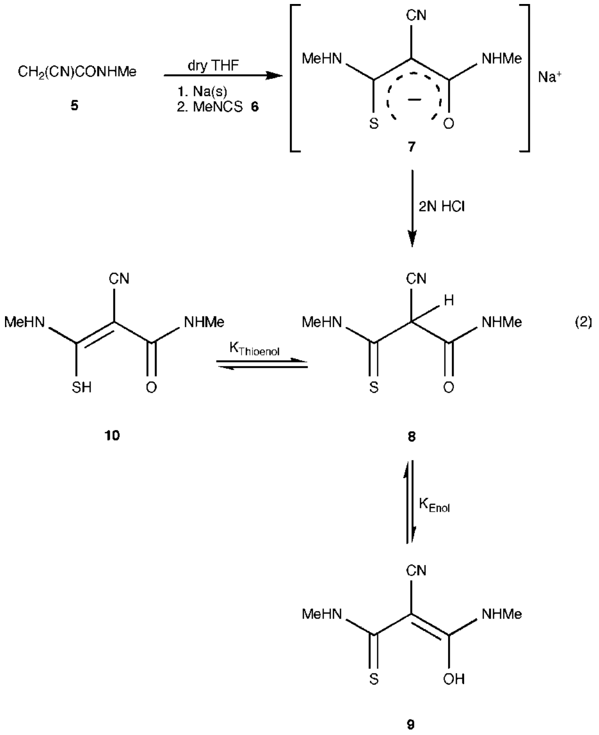


Table 1. Solvent Effect on K_{Enol}, $K_{Thioenol}$, and K_{Total} for the System **9** ⇄ **8** ⇄ **10**

solvent	% **8**	% **9**	% **10**	K_{Enol}[a]	$K_{Thioenol}$[b]	K_{Total}[c]
$CDCl_3$	22	71	7	3.24	0.27	3.51
C_6D_6	16	82	2	5.12	0.13	5.25
THF-d_8	34	66	0	1.97	≤0.01	1.97
CD_3CN	67	33	0	0.50	≤0.01	0.50
DMSO-d_6	100	0	0	≤0.01	≤0.01	≤0.01

[a] K_{Enol} = [**9**]/[**8**]. [b] $K_{Thioenol}$ = [**10**]/[**8**]. [c] K_{Total} = ([**9**] + [**10**])/[**8**].

The ^{13}C NMR spectra (see the Supporting Information) corroborated the assignments.

The **8/9/10** distributions and the derived three *K*'s are given in Table 1. The trend observed for many systems, such as a rapid equilibration and an increase in the % amide with the increase in the polarity of the solvent, is observed also here.[6,8,10] The amide is the exclusive species in DMSO-d_6. For our system, the percent of thioenol was much lower than that of the enol, and it was not observed in THF-d_8, CD_3CN, and DMSO-d_6.

Suitable crystals for X-ray diffraction were obtained by crystallization of the solid precipitated from the reaction of eq 2. Dilute solutions in the solvents were kept at rt for 24−48 h. From $CDCl_3$, the enol **9** (mp 136 °C) was obtained, and from CD_3CN, the amide **8** (mp 142 °C) was obtained.

The ORTEP drawings of **8** and **9** are shown in Figure 1, and relevant bond lengths and angles are given in Table 2. The data for **8** are for a crystal containing a single enantiomer.

A different crystal containing a racemate (**8′** in Table 2) shows very similar bond lengths and angles and somewhat different torsion angles: angle (**8**, **8′**), C(4)C(2)-

---

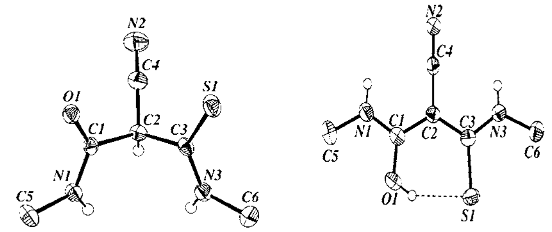
(6) Mukhopadhyaya, J. K.; Sklenak, S.; Rappoport, Z. *J. Am. Chem. Soc*. **2000**, *122*, 1325.

(7) Lei, Y. X.; Cerioni, G.; Rappoport, Z. *J. Org. Chem*. **2001**, *66*, 8379.

(8) Lei, Y. X.; Casarini, D.; Cerioni, G.; Rappoport, Z. *J. Phys. Org. Chem*. **2003**, *16*, 525.

(9) Song, J. Unpublished results.

(10) Basheer, A.; Rappoport, Z. *Kyushu International Symposium on Physical Organic Chemistry (KISPOC XI)*, Fukuoka, Japan, September 12−15, 2005; Abstr. O 01, pp 1−2.



8 **9**

Figure 1. ORTEP drawing of **8** and **9**.

C(3)S(1) (39.5, 48.9), C(4)C(2)C(1)O(1) (−36.1, −25.7), C(5)N(1)C(1)O(1) (−2.7, −0.9), C(6)N(3)C(3)S(1) (0.7, −0.2).

9 **10** (3)

The amide displays elongated C−C(═O)NC bonds of 1.544 and 1.528 Å compared with a (normal) C−C(═O)-NC bond of 1.506 Å,[11] presumably due to electrostatic and steric repulsions between the CN and CO or CS electron-withdrawing groups. An interesting feature is that, despite the fact that the hydrogen bond is unsymmetrical and the O−H bond of 0.797 (19) Å is 1.3 Å shorter than the S···H bond, the two C−C bonds C(1)C(2) and C(2)C(3) are nearly of the same length, which is between those for a single and double bond length. In the enol structure **9**, the C(1)C(2) bond should be a formal double bond, which in many similar push−pull enols is elongated up to ca. 1.42 Å[6,8,10,12] due to the dipolar (MeNHCS)(CN)C^-−C^+(OH)NHMe contribution to the ground-state structure of **9**. However, the shortening of the C(2)C(3) bond from 1.535 to 1.434 Å in **8**, even if C(2) is sp^3 in the amide and sp^2 in the enol, indicates that the C(2)C(3) bond resembles the C(1)C(2) bond and raises the possibility that a rapid reversible migration of the enolic OH to the S, that is, between hydrogen-bonded enol **9** and thioenol **10** (eq 3), is responsible for the averaging of the C−C bond lengths. An alternative resonance-stabilized hydrogen bond in **9** without hydrogen migration was suggested by a reviewer. The nature of the hydrogen bond in solution was discussed[10] and will be further discussed in a future publication.

Table 2. Bond Lengths (Å) and Angles (deg) for **8**, **8′**, and **9** at 173(1) K

	8	**8′**	**9**
C(1)−C(2)	1.544(3)	1.528(3)	1.4277(18)
C(2)−C(3)	1.535(3)	1.537(3)	1.4348(19)
C(2)−C(4)	1.471(3)	1.461(4)	1.4213(19)
C(1)−O(1)	1.231(3)	1.228(3)	1.3120(18)
C(3)−S(1)	1.662(2)	1.647(2)	1.7171(14)
C(1)−N(1)	1.323(3)		1.3185(19)
C(3)−N(3)	1.317(3)		1.3278(18)
C(4)−N(2)	1.131(4)		1.1470(19)
O(1)−H			0.797(19)
S(1)···H			2.131(18)
C(1)−C(2)−C(4)	110.0(2)	110.5(2)	116.27(12)
C(3)−C(2)−C(4)	112.0(2)	111.1(2)	118.30(12)
C(1)−C(2)−C(3)	108.05(18)	109.07(03)	125.43(12)
C(2)−C(1)−N(1)	114.84(18)	114.9(2)	121.92(13)
C(2)−C(3)−N(3)	113.3(2)	113.1(2)	118.32(12)

However, despite the usual difficulty to precisely locate the hydrogens, the hydrogen seems to be more bound to the O than to the S. An imbalance between the averaging of the two C−C bonds and that of the two O−H bonds in analogous enols of cyanomalonamides[13] was found to be temperature dependent. In the only structure of the thioenol of amide known to us, that of Meldrum's acid substituted at C5 by a ═C(SH)NHPh moiety,[14] the S−H and C−S bond lengths are 1.22 and 1.739 Å, respectively; that is, the C−S bond length does not differ much from that in **9**, but the S−H bond is much shorter. In **9**, the C−S bond length of 1.717 Å is between the value above and the average C═S value of 1.671 Å,[11] suggesting some thioenol character. We also note that, for the structures of the two β-thioxoketones, determined by X-ray diffraction, the enethio form is known in solution, but in the solid, the enol is that of the carbonyl group.[15]

We note that the C(2)C(4) bond in **9** of 1.421 Å (the average C═C−C≡N bond length is 1.427 Å[11]) is very close to those of C(1)C(2) and C(2)C(3).

Even if eq 3 applies, this is the first case where a pair of isomeric amide/enol of amide (or thioamide) was isolated as distinct species. In our case, the crystallizing species from the two solvents tried is the major species observed in solution in this solvent. This is not a general case. We tried to crystallize several related systems from solvents of different polarity, but so far, we always isolated only the same species from all of them. Thus, crystallization of *i*-PrNHCOCH(CN)$CONMe_2$ from $CHCl_3$, EtOAc/petroleum ether, or DMF−H_2O gave only the amide structure, although in $CDCl_3$ solution, the enol consists 80% of the mixture, whereas only the amide was observed in DMF solution. The close analogue PhNHCOCH(CN)$CONMe_2$ displays 80% enol in $CDCl_3$ solution, and crystallization from $CHCl_3$ gives the enol.

When MeNHCSCH(CN)$CONMe_2$, the analogue of **8**, was crystallized from $CDCl_3$, THF-d_8, or CD_3CN, which display 88, 96, and 100% amide in solution, only the solid amide was obtained. Only the amide of *p*-$MeOC_6H_4$NHCOCH-(CN)$CONMe_2$ was crystallized from $CDCl_3$ and CD_3CN,

---

[11] Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.

[12] Lei, Y. X.; Casarini, D.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2003**, *68*, 947.

[13] Rappoport, Z.; Basheer, A. *17th IUPAC Conference on Physical Organic Chemistry*, Shanghai, China, August 15−20, 2004; Abstr. IL-10, p 84.

[14] Basheer, A.; Rappoport, Z. Unpublished results.

[15] Gilli, G.; Bertolasi, V. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 1990; Chapter 13, pp 725−726.

although the corresponding amide comprises 20 and 87%, respectively, in their solution.

Acknowledgment. We are indebted to Dr. Shmuel Cohen from the Department of Inorganic and Analytical Chemistry, The Hebrew University, for the X-ray structure determination, and to the Israel Science Foundation for support.

Supporting Information Available: The full crystallographic data of **8**, **8′**, and **9**, Tables S1−S3 of spectra of ^{1}H and ^{13}C NMR data, integration of signals, and the synthesis of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062322Z