Cyano-, Nitro-, and Alkoxycarbonyl-Activated Observable Stable Enols of Carboxylic Acid Amides

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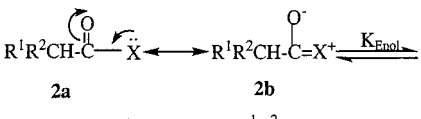
A search for the enol structures of several amides YY′CHCONHPh with Y,Y′ = electron-withdrawing groups (EWGs) was conducted. When Y = CN, Y′ = CO_2Me the solid structure is that of the enol (**8b**) $MeO_2CC(CN)$═C(OH)NHPh, whereas in solution the NMR spectrum indicate the presence of both the amide $MeO_2CCH(CN)CONHPh$ (**8a**) and **8b**. When Y = NO_2, Y′ = CO_2Et the main compound in $CDCl_3$ is the amide, but <10% of enol(s), presumably $EtO_2CC(NO_2)$═C(OH)NHPh (**9b**), are also present. When Y = COEt, Y′ = CO_2Me or Y = COMe, Y′ = CO_2Et (**10** and **11**) enolization in solution and of **11** also in the solid state occurs at the carbonyl rather than at the ester site. With Y = Y′ = CN a rapid exchange between the amide $(NC)_2CHCONHPh$ (**12a**) and a tautomer, presumably the enol, take place in several solvents on the NMR time scale. With YY′ = barbituric acid moiety the species in DMSO-d_6 is an enol of an amide although which CONH group enolizes is unknown. B3LYP/6-31G** calculations showed that the enol $(NC)_2C$═C(OH)NH_2 (**13b**) is more stable by ΔG of 0.4 kcal/mol than $(NC)_2CHCONH_2$ (**13a**) due to a combination of stabilization of **13b** and destabilization of **13a** and both are much more stable than the hydroxyimine and ketene imine tautomers. The effect of Y,Y′ and the solvent on the relative stabilization of enols of amides is discussed.

Introduction

Enols of carboxylic acids and their derivatives (esters, amides, anhydrides, and acyl halides, **1**, X = OH, OR, NRR′, OCOR, halogen) are usually unstable compared with the acid derivative **2** itself. Consequently, only a few systems with X = OH, OR, NRR′ were observed and investigated in recent years, although others were suggested as reaction intermediates.[1] Recent literature references including those to calculations of the relative stabilities of these species and several examples are given in our recent paper.[2]

Most approaches used until recently to generate observable enols of acid derivatives include nucleophilic addition to ketenes. The groups of Wirz,[3a] Kresge,[3b−f] and recently Lusztyk[3g] photochemically generated short-lived ketenes and studied their rapid hydration to **1** and the rapid **1** → **2** isomerization by fast detection methods. The groups of Hegarty[4a] and Rappoport[4b−d] used bulky diaryl substituted ketenes to generate sterically hindered Ar_2C═C(OH)X (X = OH, OR, NRR′), which were kinetically sufficiently long-lived to be observed by UV and NMR spectroscopies. A recent approach generated a simple enol of an amide by solvolysis of a chloroenamine.[5] However, in none of these methods K_{Enol} was found to be sufficiently high (i.e., ≥0.05) to enable observation of the enols at equilibrium.

The low stabilities and K_{Enol} values (eq 1) are attributed to a strong stabilization of the acid structure by a significant resonative electron donation of the heteroatom X in hybrid **2b**, which locate the negative charge on the electronegative oxygen. We reasoned that the enol will be similarly stabilized if the negative charge on C_β of the dipolar hybrid **1b** will be delocalized by β-electron-withdrawing groups (EWGs) R^1 and R^2.[2,6]



(1)

Indeed, nitromalonamide $O_2NCH(CONH_2)_2$, few cyclic amides and three tetracyclines having an amide group

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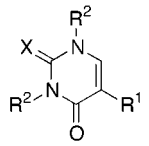
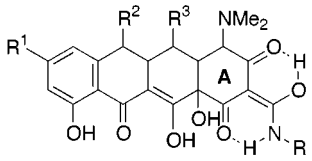
which carry β-EWGs have the enol of amide structures $H_2NCO(O_2N)C{=}C(OH)NH_2$,[7] **3a**−**d**[8] and **4a**−**c**,[9] respectively, in the solid state. This encourages us to start a systematic study of this topic, and we had already showed[2] that a 5-CONHPh-substituted Meldrum acid (MA) is enolic (cf. **5**) both in the solid state and in solution. The open chain analogue **6** has the amide structure **6a** in the solid, but in $CDCl_3$ solution it appears as ca. 95% **6a** in equilibrium with an enolic structure which may be either **6b** or a mixture of **6b** and **6c**. The diketo-activated six-membered analogues of **5** are enolic on a ring oxygen, having structures **7**.[2]



3 a-c: R^1 = Ph, OH or NO_2; R^2 = H, X = O
d: R^1 = H, R^2 = Et, X = S



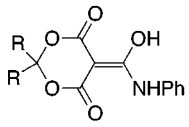
4a,b: R = R^1 = H, R^3 = OH, R^2 = Me or =CH_2
4c: R = *t*-Bu, R^1 = OMe, R^2 = R^3 = H

We had also shown that cyclopentadienes substituted by at least two vicinal CO_2Me groups, one of which on the formally sp^3-hybridized carbon, exist in the solid state and in chlorinated solvents as the enol of the tautomeric ester.[6]

In the present work we extend these works to carboxylic acid anilides activated by various combinations of the two EWGs, CN, CO_2R, NO_2, and CONHR.

Results and Discussion

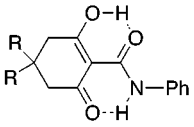
General Considerations. The two ester groups in the anilides **5** and **6** are sufficient to generate observable enols of anilides, whereas most diketo-activated systems (e.g., **7**) enolize on the nonamidic keto groups, although compounds **4** exist as solid enols of amides. Solid nitromalonamide[7] is enolic but ethyl dinitroacetate is fully in the ester form.[10] Likewise, tri(methoxycarbonyl)methane is completely in the ester form.[11] Consequently, although there are trends, which are corroborated by calculations,[2,12] at present we do not see any systematic behavior. Hence, our first stage in a more systematic search of the enol of amide structure is to screen various anilides with different EWGs.



5, R = Me

$(MeO_2C)_2CHCONHPh$ **6a** $(MeO_2C)_2C{=}(OH)NHPh$ **6b**

$(MeO_2C)C(CONHPh){=}C(OH)OMe$ **6c**



7a: R = H
7b: R = Me

Synthesis. In analogy with the preparation of **5**−**7**,[2,13] we prepared the anilides in the present work by reaction of active methylene compounds with phenyl isocyanate (eq 2). The combination of EWGs involve CN and CO_2-Me (**8**), NO_2 and CO_2Et (**9**), MeCO and CO_2Et (**10**) and EtCO, CO_2Me (**11**), CN, CN (**12**) and the barbituric acid moiety **14**.

$RO_2CCH(EWG)CONHPh$ $RCO_2C_\beta(EWG){=}C_\alpha(OH)NHPh$

8a: R = Me, EWG = CN
9a: R = Et, EWG = NO_2
10a: R = Me, EWG = EtCO
11a: R = Et, EWG = MeCO

8b: R = Me, EWG = CN
9b: R = Et, EWG = NO_2
10b: R = Me, EWG = EtCO
11b: R = Et, EWG = MeCO

$PhNHCO(EWG)C{=}C(OH)OR$

8c: R = Me, EWG = CN
9c: R = Et, EWG = NO_2
10c: R = Me, EWG = EtCO
11c: R = Et, EWG = MeCO

$PhNHCOC(CO_2Me){=}C{=}NH$ **8d**
$PhNHCOC(CO_2Et){=}NO(OH)$ **9d**

$PhCONHC(CO_2R){=}C(OH)R'$
10d: R = Me, R' = Et
11d: R = Et, R' = Me

$$CH_2(EWG)(EWG') + PhNCO \longrightarrow (EWG)(EWG')CHCONHPh \qquad (2)$$

EWG = CO_2R, EWG' = CN, NO_2, R'CO; EWG = EWG' = CN;
$CH_2(EWG)EWG' = OC(NHCO\text{-})_2CH_2$ [barbituric acid]

Also prepared was the dicyanoamide **13**, where the N−Ph of **12** is replaced by N−H, since there is literature claim that it has the enol structure, **13b**.[14] For convenience, structures **8**−**11** and **14** are written in the amide form with the suffix **a**, and enols of amides are written with the suffix **b**. Other structures, including isomeric enolic ones are written with the suffixes **c**, **d**, and **e**. The discussion below reveals the observed structures.

Structure Determination. Our previous work[2,6] had shown that the structure of the systems depends strongly

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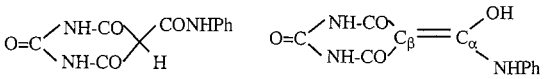
$(NC)_2CHCONHPh$ **12a**: R = Ph **13a**: R = H

HN=C=C(CN)CONHR **12c**: R = Ph **13c**: R = H

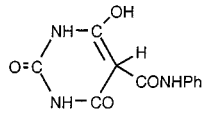
$(NC)_2C_\beta{=}C_\alpha(OH)NHR$ **12b**: R = Ph **13b**: R = H

$(NC)_2CHC(OH){=}NR$ **12d**: R = Ph **13d**: R = H

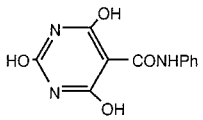


14a

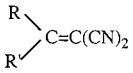
14b



14c



14d



15 a: R = Ph, R' = Me
b: R = H, R' = NHC_6H_4OMe-*p*

on the medium. Whereas the solid-state structure frequently coincides with those deduced from the spectrum in solution, there are differences in the species observed or predominate in low dielectric solvents such as $CDCl_3$ and in dipolar aprotic solvents, e.g., DMSO-d_6. Hence, whenever possible the solid-state structure was determined by X-ray crystallography, and the structure in several solvents was examined by NMR spectroscopy. Indeed, the amides of the present study had shown a variety of behaviors, depending on the phase (solid or solution), the substituents and the solvent, as detailed below.

A. The Cyanoacetate Anilide 8. (a) The Solid State Structure. All the three different groups on the central CH of the cyanoester **8**, i.e., CO_2Me, CONHPh, CN are potential tautomerisation sites; i.e., two enols (**8b**, **8c**), one amide (**8a**), and one imine (**8d**) are possible tautomers. The solid-state structure was determined by X-ray crystallography. The ORTEP drawing (Figure 1), shows a *dimeric structure of an enol of amide* **8b** in which two molecules are doubly hydrogen bonded. The amido hydrogen of one unit is hydrogen bonded to the cyano nitrogen of the other and the same applies to the other PhN−H···NC··· group. Structure **8b** generally resembles the Meldrum acid anilide **5** which also forms an enol of amide (but structural differences between **8b** and **5** are given below). The structure differs from that of **6**, the noncyclic analogue of **8** which has the amide structure **6a** in the solid. Consequently, **8b** is our second example of a solid enol of amide activated by EWG.

Selected bond lengths and angles are given in Table 1. General X-ray data, other bond lengths and angles, positional and thermal parameters and the stereoview are given in Tables S1−S4 and Figure S1 of the Supporting Information. The enolic hydrogens and H(N2), H(O1) were found in the difference Fourier map. The N(2)−H bond length is 0.97 Å and the N(1)−H hydrogen bond length is 2.07 Å, the hydrogen bond is nonlinear, the N(1)−H-N(2) angle being 146.6°. The other hydrogen is located on the "amido" oxygen O(1) in the enol form **8b** and is unsymmetrically hydrogen bonded to the C═O of a cis ester group. The O(1)−H and O(2)−H bond lengths are 1.15 and 1.48 Å and the O(1)−H-O(2) angle is 139.5°. The shorter distance of the enolic

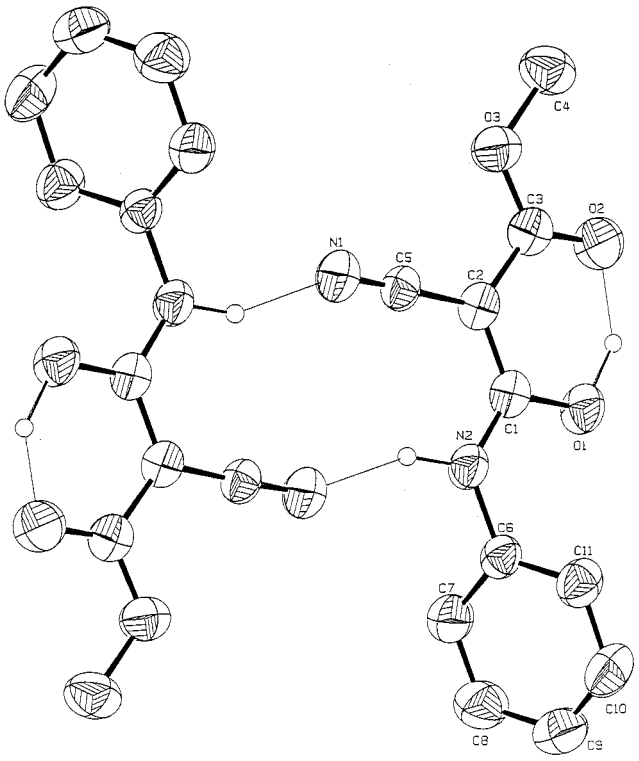


Figure 1. ORTEP drawing of **8b**.

Table 1. Bond Lengths and Angles in Solid 8b

bond	length, Å	angle	deg
C1−C2	1.394 (4)	C1−C2−C5	121.0 (3)
C1−O1	1.311 (3)	C1−C2−C3	118.5 (3)
C1−N2	1.336 (4)	C3−C2−C5	120.5 (3)
C3−O2	1.237 (4)	N2−C1−O1	116.4 (3)
C3−O3	1.324 (2)	N2−C1−C2	123.2 (3)
C5−N1	1.136 (4)	C2−C1−O1	120.4 (3)
C4−O3	1.443 (4)	C2−C3−O3	114.7 (3)
C2−C5	1.418 (4)	C2−C3−O2	122.7 (3)
C2−C3	1.436 (4)	C1−N2−C6	123.8 (2)
6 C−C in Ph	1.363 (5)−1.385 (5)	O1−H−O2	139.5
O1−H	1.15	N1−H−N2	146.6
O2−H	1.48		
N2−H	0.97		
N1−H	2.07		

hydrogen to O(1) than to O(2) indicate structure **8b** rather than the enol of ester **8c**, but a small displacement of the hydrogen concerted with a single/double bonds exchange in the formal cyclo-1,3-dioxadiene ring will convert **8b** to **8c**. Both **8b** and **5** are stabilized by an intramolecular O−H···O hydrogen bond, but in **8b** the solid enol is also stabilized by two intermolecular N−H···N≡C hydrogen bonds giving a "dimeric" structure whereas in **5** the N−H is weakly hydrogen bonded intramolecularly to the ester oxygen. This reflects a favorable distance and geometry for the inter-, rather than the intramolecular hydrogen bond to a more distant cyano nitrogen in **8b**.

Other differences between the two enols are: (a) the C(1)═C(2) bond is shorter (i.e., of higher double bond character) in **8b** than in **5** whereas the former amido carbonyl C−O bond is slightly shorter in **5**. (b) The C(2)−C(3) bond is somewhat longer in **8b** than in **5** but corresponding bond angles are not much different in **5** and in **8b**.

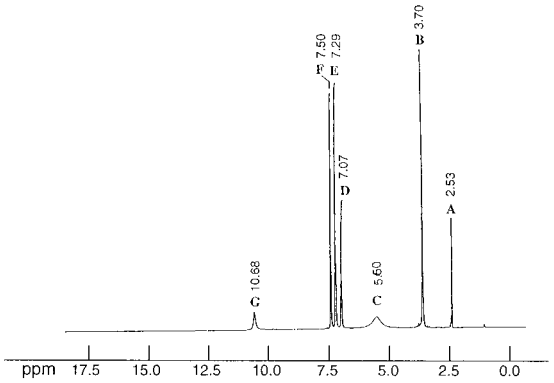


Figure 2. ^{1}H NMR spectrum of **8** in DMSO at room temperature: (A) solvent; (B) OMe; (C) exchanging CH/OH; (D−F) Ph; (G) NH.

The polar electron-withdrawal effect of CN is higher than that of a methoxycarbonyl (CO_2Et: σ_I 0.30, σ_R^- 0.34, CN: σ_I 0.56, σ_R^- 0.34)[15] but this effect is too small to account for the difference in the solid-state structures of **6** and **8**. This difference can be due to a stereoelectronic effect. The smaller and linear cyano group enables both β-substituents to be simultaneously in the double bond plane and thus to exert their maximal resonance effect in stabilizing the enol. The X-ray data support this assumption. The dihedral angles between the plane of the C═C group and its substituents and the O═C−C(2), NC−C(22), HO−C(1) and NH−C(1) planes are respectively, 0.02°, 6.6°, 1.0°, and 0.03°, i.e., the system is nearly planar. Note, however, that in the *calculated* structure of enol **6b** both ester groups are also nearly in the C═C plane.

(b) The Structure in Solution. In contrast with the unequivocal enolic structure of solid **8**, the structural assignment in solution is not obvious and is solvent-dependent.

(i) In Solutions of the Polar Solvents DMSO-d_6 and CD_3CN. In DMSO-d_6 **8** displays Me (at δ 3.70) and Ph (at δ 7.07) signals but also a broad signal at δ 5.60 (CH) and at δ 10.68 (NH), and no signal at a lower field than 15 ppm (Figure 2). The two latter signals disappear on addition of D_2O. Similar features were observed for the major species of **6** (i.e., **6a**), and hence, the structure is either mainly **8a**, or in view of the broad signal at δ 5.60, there is an exchange process involving the CH or the OH groups in a mixture in which **8a** predominates. To find out if an enol signal is not lost at room temperature due to an exchange, a DMSO-d_6 solution of the sample was heated during 30 min to 366.8 K. The solution became light orange and its ^{1}H NMR spectrum became more complex showing aliphatic signals at δ 3.21, 3.63, 3.72, 3.80, 3.89 and ca. 5.2 (broad), 6.9−7.6 (aromatic multiplet), 10.0 (singlet) and 10.4 (broad singlet), but no new signal at δ 15−18. Most of these signals were retained on re-cooling to room temperature, and we conclude that an irreversible reaction occurred on warming. This could be a cleavage reaction but it was not investigated further.

In the ^{13}C spectrum in DMSO-d_6 at room temperature there are very weak and broad C_α, C_β signals and a broad Me signal (at δ 53.0). For example, in Figure 3, C_β is not observed and the C_α signal at 164 ppm is barely observed. The only observed significant signals are for Ph and CN at δ 119.65−138.05 (Figure 3). In D_2O/H_2O the signals at δ 124.5 and for C_{ipso} broaden. This is not inconsistent with structure **8a** as the main component of a rapidly exchanging mixture. At 366.8K the spectrum fits a decomposition process since signals at 23.56, 25.96 (new) and 48.02, 52.18, 160.22, and 163.89 ppm are observed.

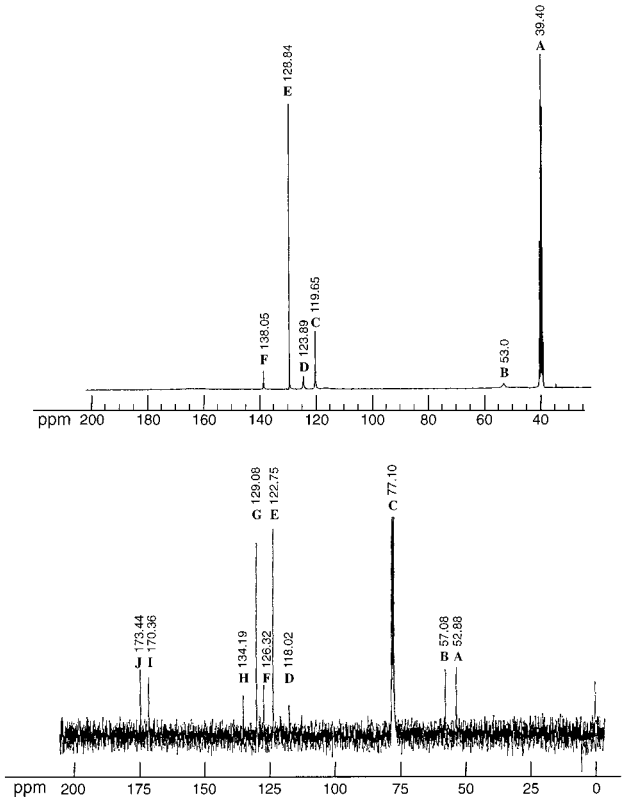


Figure 3. ^{13}C NMR spectrum of **8** in DMSO-d_6 at room temperature: (A) solvent; (B) Me; (C−F) Ph + CN. Note the trace of a very low intensity signal at δ of ca. 163.

The ^{1}H NMR spectrum in CD_3CN resembles that in DMSO-d_6 in the Me and Ph region, but there are three broad signals at δ 4.86, 8.30, and 8.85. The compound precipitates on cooling, and the only reliable information is that no new OH signal is observed at 230K immediately after cooling. On warming to 340 K, the signal at δ 8.30 disappears, the other two broad signals remain broad and other signals, mainly aliphatic, appear. Again, this may be due to decomposition.

The rt ^{13}C NMR spectrum in CD_3CN shows four aliphatic signals at 46.76−57.47 ppm, seven signals at 117.30−137.40 ppm, and three very weak signals at 158−162.5 and 171 ppm (see the Experimental Section). The coupled spectrum shows the aliphatic signals as a doublet at δ 46.76 (J = 135 Hz), two Me quartets at δ 52.36, 53.96, and a singlet at δ 57.47. These are consistent with a mixture of **8a** (CH at δ 46.76, and a Me) and **8b** (>C═ at δ 57.47 and a Me). In the aromatic region the signals are for CD_3CN (strongest) and for Ph + CN of **8**; i.e., there is only one extra signal over those expected for a single species. The low field signals are too weak to give reliable information, although their low intensity may indicate an exchange process.

(ii) In Chlorinated Solvents. In $CDCl_3$ at room temperature, the ^{1}H NMR spectrum is deceptively simple. A CH signal is not observed at ca. 4.7 whereas a lower

(15) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; pp 154 and 157.

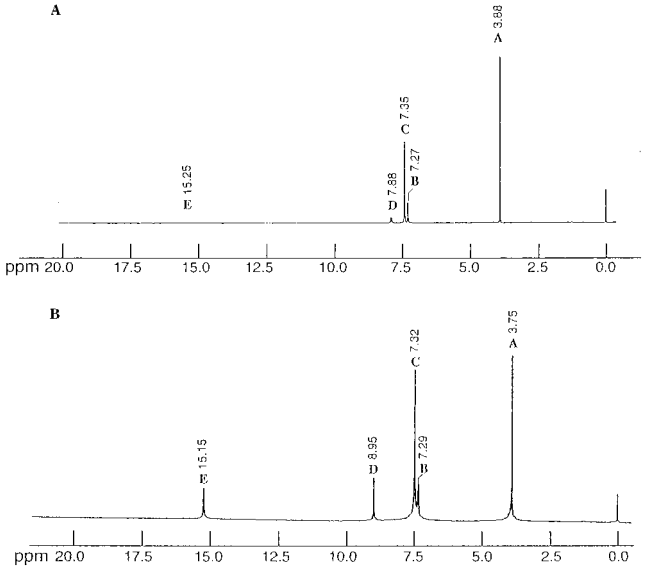


Figure 4. ^{1}H NMR spectrum of **8** in $CDCl_3$ (A) at room temperature and (B) 220 K: (A) OMe; (B,C) Ph; (D) NH; (E) OH.

field signal at ca. 15.4 ppm is mostly (but not always) observed in addition to a Me singlet at 3.88 ppm, a Ph multiplet at 7.23−7.48 and a broad 0.8H signal at 7.88 (N−H). A broad signal may be hidden below the aromatic signal (Figure 4A). On adding D_2O, an HDO signal at δ 4.73 replaces the δ 7.75 signal. The lack of characteristic signals for the amide form **8a** and the weak OH signal suggests that enol **8b** is present, but the broadening of the latter signal suggest that **8b** exchanges with another isomer (possibly with catalysis by impurities in the solvent). However, addition of traces of HCl as a catalyst for the exchange, did not change the appearance of the spectrum. To slow a possible exchange the spectra were therefore measured at 243 and 220 K. Most signals were slightly shifted, but the small signal at δ 7.88 was replaced by two new signals at δ 8.70 and 15.27 (243 K) [or 8.95 and 15.15 ppm at 220 K]. These sharper signals were ascribed to the NH and OH protons, respectively, of enol **8b** (Figure 4B). Since no CH signal was observed at 220 K we conclude that at room temperature **8b** is the main component of the mixture and it rapidly exchanges with a small amount of **8a**, **8c**, or **8d**. This is supported by the single carbonyl signal in the IR at 1642 cm^{-1}, which is consistent with the highly conjugated ester group of the push−pull alkene **8**, and with the OH signal at 3192 cm^{-1}.

The coupled ^{13}C NMR spectrum in $CDCl_3$ shows a Me at δ 52.59(q), a CN at δ 116.22(s) and Ph signals at δ 112.69−134.91 and signals at 57.74(s), 171.11 and 173.75 ppm. The former is a singlet in the coupled spectrum and can be assigned to the *C*H of **8a** only if the associated proton exchanges rapidly on the NMR time scale. Alternatively, the structure could be **8b**, if δ 57.74 is assigned to C_β in C_β(CN)CO_2Me in the push−pull ethylene. Since this signal is still a singlet at 220 K, when the OH group is observed and exchanges much more slowly, this assignment is more likely. The low field signals are then C_α at 171.11 ppm and an ester carbonyl at 173.35 ppm, and $\Delta C_{\alpha\beta}$ = 113.37 ppm. This large value is consistent with the high $\Delta C_{\alpha\beta}$ found for **5**. On adding 1:1 D_2O/H_2O the C_β, C_o, C_{ipso} and C_α signals split by 25, 8.3, 1.5, and 7 Hz, due to isotope induced shifts. The uncoupled

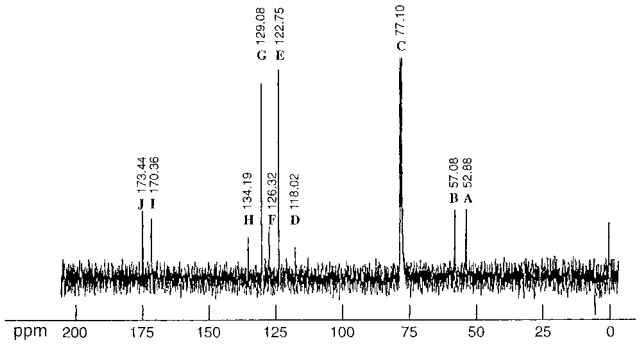


Figure 5. ^{13}C NMR spectrum of **8** in $CDCl_3$ at 220 K: (A) OMe; (B) *C*(CN)CO_2Me; (C) solvent; (D−H) Ph + CN; (I,J) C_α and CO.

spectrum at 220 K, which differs only slightly ($\Delta C_{\alpha\beta}$ = 113.28 ppm) is given in Figure 5.

A single C═O signal appears in the IR spectrum in $CDCl_3$ at 1642 cm^{-1}.

The enol **8b** is also observed in CCl_4 and $Cl_2CDCDCl_2$ where the ^{1}H NMR spectra at room temperature resemble that in $CDCl_3$. In CCl_4 the signals are at δ 3.03, 4.83 and a very weak OH signal appears at 16.25 ppm. In $Cl_2CDCDCl_2$ the room temperature ^{1}H NMR spectrum shows Me, Ph and NH signals, a broad OH signal at δ 15.40 and a narrower signal at 7.72 ppm.

The solid state ^{13}C spectrum shows Me signals at ca. 36.50, Ph + CN signals at 123.7−132.8 and signals at ca. 171 ppm.

B. The Nitro Ester Activated Anilide 9. The behavior of ethyl anilidoacetate **9** in $CDCl_3$ at room temperature resembles that described for the diester **6**. The main signals are CH (δ 5.91), NH (δ 8.99), Et (δ 1.38, 4.43), and Ph (δ 7.23−7.56) signals. However, a very weak (<0.1H) signal at δ 16.66, which is the only one disappearing rapidly in D_2O is also sometimes (but not always) observed. When a solution which does not show this signal is cooled to 220 K four very small singlets appear: two are of nearly the same intensity at δ 19.32 and 12.03 and somewhat more intense signals are at 16.84 and 11.94. The signal at δ 9.43 (presumably the N−H of **9a**) which is ca. 35−50-fold more intense than these signals, becomes sharper. Expansion shows also a very broad signal centered at ca. 15 ppm. Small Ph multiplets and Me signals accompany the major corresponding signals and the CH_2 signal is broadened. We conclude that the main compound in $CDCl_3$ is the amide, **9a**. The IR peaks at 1754, 1677 cm^{-1} are consistent with the C═O stretching vibrations of **9a**. However, the appearance of a <0.1 H signal at δ 16.66 which rapidly disappears on addition of D_2O, suggests the presence of an additional minor enolic species at room temperature. Moreover, the observation at 220 K of *two* signals at δ <16.84 (OH) and *two* signals at ca. 12 ppm (NH) and additional small Me and Ph signals, superimposed on these of **9a** indicate the presence of *two* enols of amides, consisting together <10% of the mixture. There is no further data to decide if these are **9b** and **9c** (or even **9d**) or two geometrical isomers of either of these species.[21] Exchange between **9a** and enol forms is slower than for **5**.

Ethyl dinitroacetate was reported before sensitive NMR spectrometers were available, to be in the ester form.[10] It seems worthwhile to reinvestigate this system

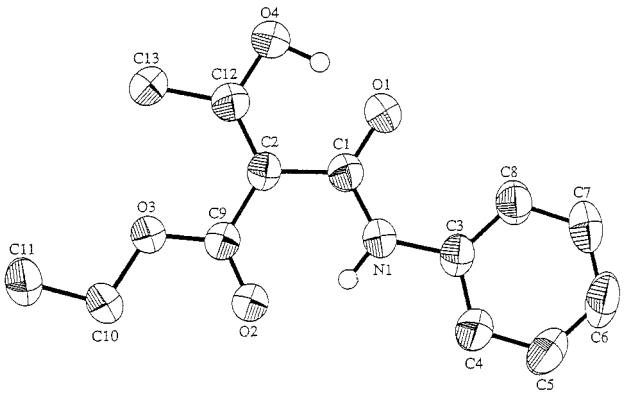


Figure 6. ORTEP drawing of **11d**.

Table 2. Bond Lengths and Angles for 11d

bond	length, Å	angle	deg
C1−C2	1.473 (4)	C(2)−C(12)−O(4)	120.7(3)
C(1)−O(1)	1.251 (3)	C(2)−C(12)−C(13)	128.0 (3)
C(2)−C(12)	1.377 (4)	O(4)−C(12)−C(13)	111.3 (3)
C(2)−C(9)	1.461 (4)	C(1)−C(2)−C(9)	119.4 (2)
C(12)−O(4)	1.320 (4)	C(1)−C(2)−C(12)	117.6 (3)
6 Ph C−C bonds	1.369 ± 0.010[a]	C(9)−C(2)−C(12)	123.1 (2)
C(9)−O(2)	1.208 (3)	O(1)−C(1)−C(2)	120.7 (3)
C(12)−C(13)	1.483 (4)	O(1)−C(1)−N(1)	120.5 (3)
C(1)−N(1)	1.335 (4)	6 Ph CCC	120.0 ± 1.0
C(3)−N(1)	1.411 (3)	O(1)−H−O(4)	161.3[a]
O(4)−H	0.98	O(2)−H−N(1)	140.5[a]
O(1)···H	1.47	O(4)C(12)C(13)/ C(1)C(2)C(9)[b]	2.25
N(1)−H	0.91		
O(2)···H	1.83	C(1)C(2)C(9)/ C(2)C(1)O(1)[b]	0.46
		N(1)C(1)O(1)/ C(9)C(2)O(1)	0.46

[a] The shorter bond is C(6)−C(7): 1.345 (6) Å. [b] Dihedral angle.

although we noted here and earlier[2] that enolization on an ester is less probable than on an amide. Crystals of **9** suitable for X-ray crystallography were not obtained and the enols concentrations are too small to draw further conclusions.

Again, there is less enol in DMSO-d_6 where the spectra are consistent with structure **9a**. In the ^{1}H NMR spectrum no OH signal is observed, but the relative intensity of the CH proton is <1. In the ^{13}C NMR spectrum both carbonyls are relatively upfield (154.44, 161.84). The situation resemble that for **6**.

C. The Keto Ester Derivatives 10 and 11. The isomers **10** and **11** differ in the locations of the Me and Et groups on the acyl and ester moieties. The ^{1}H NMR spectra in $CDCl_3$ of both contain in addition to the aliphatic and Ph signals N−H signals at δ 11.2−11.5 and temperature-dependent O−H signals at δ 8.2−18.4, which disappear rapidly on shaking with D_2O. These spectra are not an unequivocal structural probe. The C═O group of **10** and **11** is a much more favorable enolization site than the amido or the ester group, and the very low field OH signal and the IR spectrum which display OH stretching absorptions are accounted for by the enol structures of amide (**10b**, **11b**), of ester (**10c**, **11c**) or of a ketone (**10d**, **11d**), but not by structures **10a**/**11a**.

The ^{13}C NMR spectra of either **10** or **11** in $CDCl_3$ display signals for two Me, one CH_2, four C−Ph carbons, one at ca. δ 94, a singlet and a narrow multiplet at the 168.8−171 region and a single C═O signal (quintet, J = 5−6 Hz) at δ 92 (**10**) or 196.2 (**11**) (see Experimental Section). The structures are **10b**/**11b** or **10c**/**11c** if C_α is at the δ 70 region or **10d**/**11d** if C_α appears at a lower field than 190 ppm. Since C_α of **5** is at the δ 170 region, but δ C(OH) of **7** is at the δ 190 region, the assignment is difficult. Analogies with the solid-state structure of **11**, which is the amido-substituted carbonyl enol, **11d**, and with the derivative **7**, and the calculated much higher pK_{Enol} values for simple carbonyls than for simple amides and esters suggest that the structures are **10d**/**11d**. C−H correlation spectra of **11** had shown long-range correlations between the OH and the CH_2, C_β, CO and the δ 170 signal.

Solid State Structure of 11. To unequivocally determine the structure of **11**, its X-ray diffraction was determined. The ORTEP structure (Figure 6), shows that the solid-state structure is **11d**. Selected bond lengths and angles are in Table 2 and general X-ray data, other bond lengths and angles, positional and thermal parameters are in Tables S5−S8 and the stereoview is in Figure S2 of the Supporting Information.

The following features are relevant: (a) An almost normal C(1)−C(2) bond (1.473 Å) for an sp^2−sp^2 bond. (b) The C(2)−C(12) bond length of 1.377 Å is somewhat longer than a normal C═C bond and shorter than the C(2)−C(9) bond of 1.461 Å. (c) An O(4)−H bond of 0.98 Å, a C(12)−O(4) bond of 1.320 Å and a C(1)−O(1) bond of 1.251 Å and a O(1)−H distance of 1.47 Å. The O(1)−H−O(4) angle is 161.3°. (d) N(1)−H and O(2)−H bonds of 0.91 and 1.83 Å and an N(1)−H−O(2) angle of 140.5°.

D. The Malononitrile Derivatives 12 and 13. (a) *N*-Phenylcarbamidomalononitrile 12. In the absence of a solid-state structure of **12** only the situation in solution was investigated. Compound **12** displays only Ph and NH protons in the ^{1}H NMR spectra in both $CDCl_3$ and DMSO-d_6 (Figure 7). The absence of either a CH or an OH signal can reflect an ionization−dissociation of the carbon acid or a broadening due to exchange of the amide **12a** and the enol **12b**. The coupled ^{13}C NMR spectrum in DMSO-d_6 (Figure 7) displays singlets at 34.38 and 167.61 ppm. Since the low field carbon, which should be due to C_β of the $C_\beta H(CN)_2$ group of the amide form **12a**, is a singlet, a rapid exchange, a dissociation of H_β or structure **12b** are possible interpretations. Since the cyano groups appear as a singlet at 121.01 ppm, the signal at δ 167.61 may be either a C═O (of **12a**) or C_α (of **12b**) or an average of both if C_α is involved in a rapid exchange. The low solubility in $CDCl_3$ and the high mp of DMSO prevented a study under conditions of a slower exchange achieved by cooling. However, the ^{1}H NMR spectrum in CD_3CN, where the solubility is higher shows at room temperature NH and Ph signals, but also a broad signal at 5.15 ppm, indicating that an exchange process takes place. On cooling the CD_3CN solution to 233 K, the signal (now at 5.22 ppm) sharpens. On addition of D_2O the NH and the δ 5.15 signals disappear immediately, and hence the latter is ascribed to the exchanging CH/OH proton of **12a**/**12b**. Assuming that the δ(OH) of the proton of **12b** is at δ 15−18 as with **6b**, **8b**, and **9b** and the δ(CH) signal of **12a** is at δ 3−5, the observed δ suggests that **12a** is the major component of the mixture in CD_3CN. Consequently, the trend found for **12** resembles that for **9**, i.e., in a higher dielectric constant solvent the amide/enol equilibrium is shifted in the amide direction.

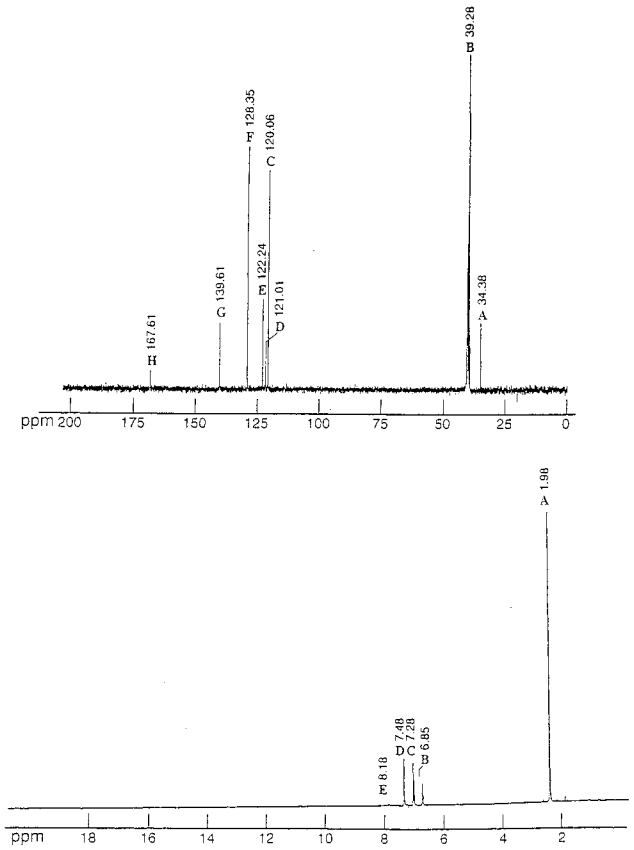


Figure 7. NMR spectrum of **12** in DMSO-d_6 at room temperature. (Bottom) ^{1}H spectrum: (A) CH(CN)$_2$; (B−D) Ph; (E) NH. (Top) ^{13}C spectrum: (A) *C*(CN)2; (B) solvent; (C−F) Ph + CN; (H) CO.

Compounds **15a** and **15b** were considered as ^{13}C NMR models for enol **12b**. In $CDCl_3$ **15a** displays signals at δ 24.05 (Me), 84.38 (C_β), 112.58, 112.68 (CN), 127.16, 128.89, 132.05, 135.70 (C−Ar) and 175.47 (C_α); $\Delta C_{\alpha\beta}$ = ca. 91 ppm. **15b** which is little soluble in $CDCl_3$ displays signals in DMSO-d_6, at 50.23 (*C*(CN)$_2$), 55.26 (Me), 114.39, 114.46, 116.68, 119.53, 132.43 (Ar + CN), 155.58 (d, J = 176 Hz, C_α), 156.82 (C_{ipso} to OMe); $\Delta C_{\alpha\beta}$ = 105.35 ppm. Although δ C_β values are at a very low field, C_β in **12** is at a much higher field (δ 34.38 in DMSO-d_6) and hence $\Delta C_{\alpha\beta}$ = 133.23 ppm is higher than in **15a** and **15b**. This reflects the much higher zwitterionic character of **12b** than of **15**.

The compound decomposes on standing in solution since the relative intensity of the two small signals observed at δ 2.09 and 2.20 on dissolution increase consistently with time on standing for several days.

(b) Dicyanocarbamidomethane, 13. The literature hints that solid **13** is enolic (**13b**).[14] Moreover, the corresponding esters (NC)$_2$CHCO$_2$R display ^{13}C NMR signals for both the ester and enol species.[16] On the basis of the enolic structure of solid **8b**, the presence of enol **12b** in an exchanging mixture in solution, the larger tendency of amides to enolize compared with esters and the ability of two cyano groups to be simultaneously accommodated in the C−C=C plane, an enolic structure for **13** is expected. However, the sample of **13** obtained from its salt by ion exchange according to the literature[14] gave differing microanalysis results and the HRMS showed the presence of one water molecule. The compound is slightly soluble in DMSO-d_6 and its ^{1}H NMR spectrum shows a broad, concentration-dependent signal at δ 5.58 (which shifts to δ 7.94 on dilution), a small signal at δ 7.93 and very small signals at δ 2.71 and 2.94. The coupled ^{13}C spectrum [singlets at 33.96 (*C*(CN)$_2$), 119.02 (CN) and 175.58 (C_α or CONH$_2$)], is consistent with the enol structure **13b**. These δs shift somewhat with different batches of solvents (cf. Experimental Section) which we ascribe mainly to temperature-dependence of the δs and different amounts of water. Due to the difficulties mentioned, the structural assignment is only tentative and the data were supplemented by theoretical calculations.

E. The Barbituric Acid Anilide 14. Due to low solubility in $CDCl_3$, the spectra of **14** were taken only in DMSO-d_6 at room temperature. The ^{1}H NMR spectrum displays major Ph protons at δ 7.20, 7.42, and 7.51 and signals at δ 11.51 and 11.96 which disappear on shaking with D_2O and are ascribed to the NH protons. There are additional small (ca. 0.06H) Ph proton signals at 7.45, 7.26 (t), and 6.94 (t) ppm. The ^{13}C NMR spectrum (cf. Experimental Section) displays 10 signals including seven aromatic protons at 117.97−135.80 of which three are small, having 0.05−0.07 of the intensity of the main signal. The highest field signal is at δ 80.26, ascribed to C_β and the two lower field signals than C_{ipso} are at δ 148.47 and 168.70, ascribed to NHCO signals.

In addition to the amide (**14a**) and enol (**14b**) tautomers, enolization of a ring amide is another option, especially since a triple enolization, two of the ring NHCO moieties and one of the keto−enol type will give the aromatic 4-anilido-2,4,6-pyrimidinetrione **14d**.

There are too many signals for a single compound in the ^{1}H and ^{13}C NMR spectra which indicate the presence of two Ph rings. The major compound displays signals for a Ph, a CONH and a carbon (C_β), which is formally substituted by three EWGs and uncoupled to a proton. The absence of coupling and the appearance of at most two CONHR carbonyls exclude the tetra-amide structure **14a**, whereas the absence of an observable OH signal suggests that if an enol is present it exchanges rapidly with an isomeric species. The enols could be **14b** and **14c**, both having two types of amide NH groups. In view of the trioxo structure of barbituric acid[17] we believe that the ureido moiety does not enolize and exclude **14d**. In 5,5-diethylbarbituric acid the C2 and C4 CO groups are displayed at 149 and 173 ppm, respectively,[18] and in analogy we ascribe the signals at δ 148.47 and 168.70 to the C2 and C4 carbonyls of **14**. Without further experiments we can only conclude that an enol of an amide, either **14b** and **14c**, is present in DMSO-d_6 solution.

Theoretical Calculations. The relative energies of the four isomers of **13**, i.e., the amide **13a**, the enol **13b**, the ketenimine **13c** and the hydroxyimine **13d** were calculated by using the density functional theory hybrid method B3LYP/6-31G**.[19,20] Full optimization was performed, and zero point energies and vibrational frequencies were calculated. The ΔH and ΔG values for the interconversion of the most stable conformer of each

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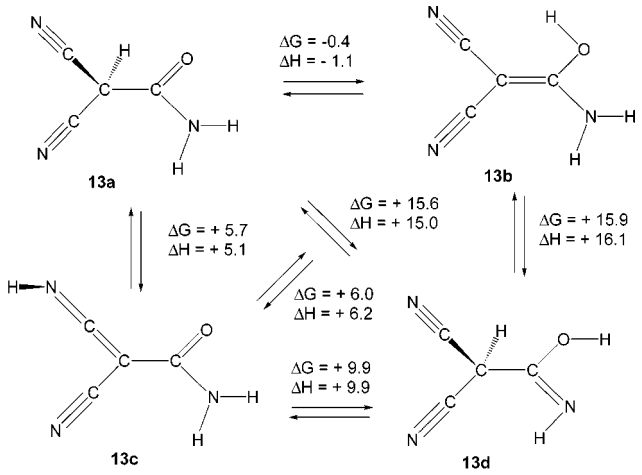
Chart 1



isomer (i.e., their relative stabilities) are given in Chart 1 and absolute energies of the isomers and other species used in the calculation are given in Table S9 of the Supporting Information.

Calculation of the structures of dicyano(carbonylamido)methane **13a** and its isomers had given several minima. The most stable structure is the enol of the amide **13b**, whose syn conformer (C_s) is more stable than the gauche conformer by 7.3 (ΔG) and 7.1 (ΔH) kcal/mol. The gauche (H/CO) "amide" structure **13a** (which is more stable than the anti H/CO conformer **13a′** by 4.3 (ΔG) or 3.1 (ΔH) kcal/mol), is 0.4 (ΔG) and 1.1 (ΔH) kcal/mol less stable than **13b**. Both isomers are much more stable than the two stable keteneimine structures **13c** and **13c′**. Of these, **13c** having the keteneimino moiety anti to the NH_2 group is more stable than the syn conformer **13c′** by 3.9 (ΔG or ΔH) kcal/mol, and 6.0 (ΔG) and 6.2 (ΔH) kcal/mol less stable than **13b**. The least stable is the enol imine form **13d**, which is 15.9 (ΔG) and 16.1 (ΔH) kcal/mol less stable than the planar **13b** (with dihedral angles of 0° or 180°). The geometries of **13a**−**d** are given in Chart 2 and the structures and relative energies of all the stable conformers of **13a**−**c** and the two more stable conformers of **13d** vs the most stable conformer of each species are given in Chart 3.

Eight stable conformers were found for **13d**. Their designations involve two descriptors. The first one relates to the conformation of the O−H group in relation to the single bond, and the second to the conformation of the C−C═N−H moiety. The most stable conformer is **13d**-*anti*-*syn*-1 which differs from **13d**-*anti*-*syn*-2 in the conformation at the $CH(CN)_2$ group. Likewise, there are two *anti*-*anti*, two *syn*-*anti*, and two *syn*-*syn* conformers. Their structures and relative energies are given in Chart 4. The order of stabilities is *anti*-*syn*-1 > *anti*-*syn*-2 > *anti*-*anti*-2 > *syn*-*anti*-2 > *anti*-*anti*-1 > *syn*-*anti*-1 > *syn*-*syn*-1 > *syn*-*syn*-2. The energy difference between the more stable and least stable conformers is 8.1 kcal/mol

Chart 2

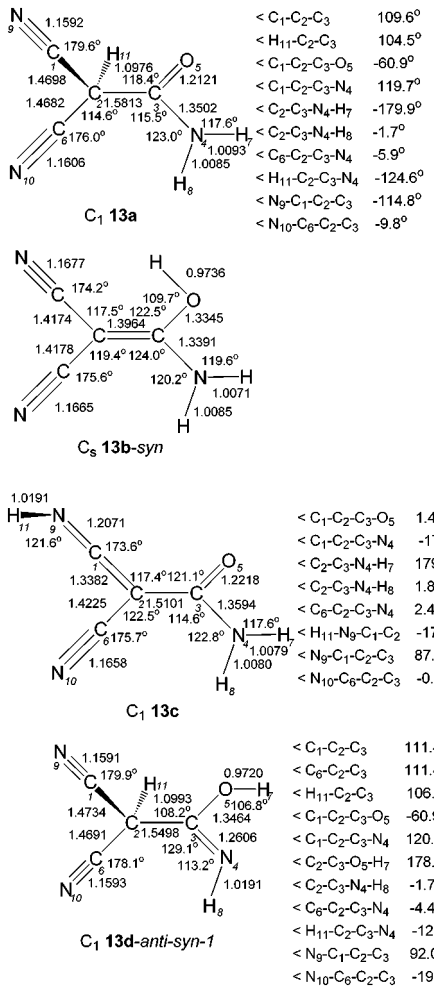
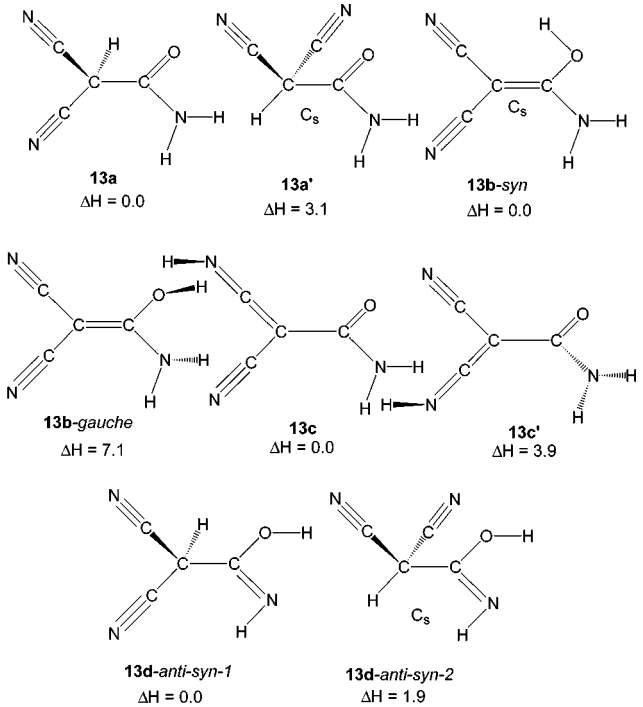


Chart 3



(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andress, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *GAUSSIAN 94*, Revision C.2; Gaussian Inc.: Pittsburgh, PA, 1995.

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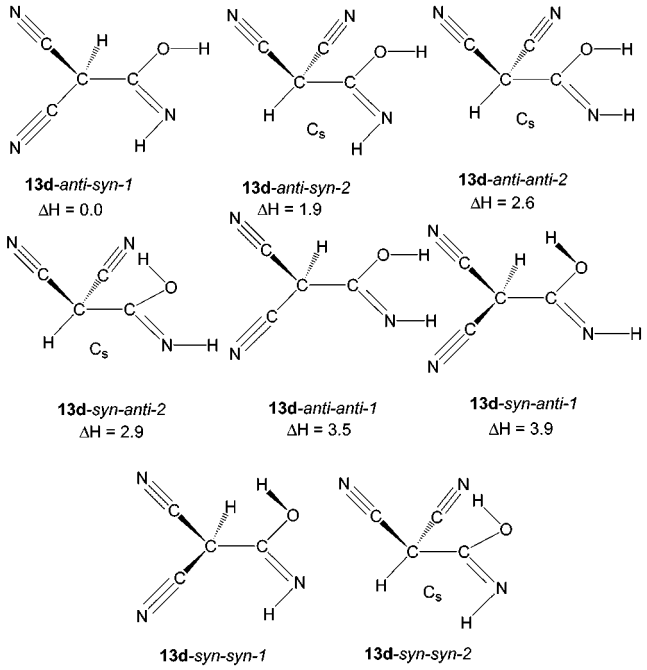
(21) **Note added in proof:** Based on analogy with the enols $ArNHC(OH)═C(CO_2R)CO_2R'$ where R and/or R′ contain fluorine substituents (Lei, Y. X., unpublished results), the species observed at 220 K are the *E*- and *Z*-isomers of **9b**.

Chart 4



and steric effects play an important role in this difference. In the most stable conformer the $C_\alpha-O-H$ is anti, i.e., remote from the small C_β-H substituent and the C−O bond bisect the HCCN angle. In the least stable conformer the C−O bond bisects the NCCCN angle and the *syn*-OH is close to a larger cyano group.

In the two =C(OH) structures, **13b** and **13d**, the O−H and N−H hydrogens are too far from the cyano group to form hydrogen bonds. In **13b** the O−H points in the direction of the CN but its distance from the nitrogen is 2.64 Å. In **13d** the distance between the imino hydrogen and the corresponding cyano nitrogen is 2.86 Å. Moreover, the orientation of the cyano nitrogen lone pairs in relation to the O−H and N−H bonds do not enable the formation of hydrogen bonds.

The qualitative order of stability of the isomers of **13** resembles that calculated for **5**: enol > amide > hydroxyimine. However, the **13b**−**13a** energy difference of ΔG = 0.4 kcal/mol is much smaller than that for **5**, despite the planarity of **13b**. This result is consistent with our conclusion that both species of **12** coexist in solution; i.e., on accepting an error of a few kcal/mol the calculations on the parent compound **13** reflect the behavior of the corresponding anilide **12** in solution. Again, the syn C=C−O−H conformers are appreciably stabilized compared with the gauche conformers.

The difference between systems **5** and **13** may mainly reflect the absence of intramolecular hydrogen bonding in **13b**, where the enolic hydrogen is too far away from the cyano nitrogen even in the favored *syn*-C=C−O−H conformation. In contrast with the amide/enol differences, the amide/imine (*anti*-H, OH) differences in the two systems are large but not differ much, being ΔG = 15.6 kcal/mol for **13a/13d** and 13.9 kcal/mol for the corresponding two species of **5**. Proton transfer to the cyano nitrogen to give **13c** is 6.0 kcal/mol more expensive than to the oxygen.

To evaluate the effect of the cyano groups on the equilibria of isomers **13a**, **13b** and **13d** we calculated ΔH values for the isodesmic reactions 3a−5a with methane as the reference and 3b−5b with ethylene as the reference. Analogous isodesmic reactions are not available for **13c**.

$$(NC)_2C{=}C(OH)NH_2 + CH_4 \rightleftharpoons H_2C{=}C(OH)NH_2 + H_2C(CN)_2 \qquad \Delta H = 27.7 \text{ kcal/mol} \quad (3a)$$

$$(NC)_2CH{-}C(NH_2){=}O + CH_4 \rightleftharpoons H_3C{-}C(NH_2){=}O + H_2C(CN)_2 \qquad \Delta H = -1.0 \text{ kcal/mol} \quad (4a)$$

$$(NC)_2CH{-}C(OH){=}NH + CH_4 \rightleftharpoons H_3C{-}C(OH){=}NH + H_2C(CN)_2 \qquad \Delta H = -3.1 \text{ kcal/mol} \quad (5a)$$

$$(NC)_2C{=}C(OH)NH_2 + H_2C{=}CH_2 \rightleftharpoons H_2C{=}C(OH)NH_2 + H_2C{=}C(CN)_2 \qquad \Delta H = 17.0 \text{ kcal/mol} \quad (3b)$$

$$(NC)_2CH{-}C(NH_2){=}O + H_2C{=}CH_2 \rightleftharpoons H_3C{-}C(NH_2){=}O + H_2C{=}C(CN)_2 \qquad \Delta H = -11.7 \text{ kcal/mol} \quad (4b)$$

$$(NC)_2CH{-}C(OH){=}NH + H_2C{=}CH_2 \rightleftharpoons H_3C{-}C(OH){=}NH + H_2C{=}C(CN)_2 \qquad \Delta H = -13.8 \text{ kcal/mol} \quad (5b)$$

From the pair of isodesmic reactions 3b and 4b (ΔH = 17 and −11.7 kcal/mol, respectively), the stabilization by β-$(NC)_2$ of the enol over the amide is 28.7 kcal/mol, sufficient to overcome the 27.6 kcal/mol destabilization of the parent acetamide/1-aminoethenol system.[12] This large effect is mainly due to stabilization of the enol by the dipolar interaction shown in **1b**, but also to a significant destabilization of the amide form, presumably due to a repulsive interaction between the electronegative CN and CO dipoles. This destabilizing effect of the β-substituents is superimposed on the carbonyl stabilization by the substituent X. Hence, introduction of two β-cyano groups increase K_{Enol} by simultaneously stabilizing the enol (60% of the effect) and destabilizing the amide form (40% of the effect). A combination of effects was previously calculated for the **6a**/**6b** system except that the relative contribution of the enol stabilization effect was higher (86%).

Another conclusion from the isodesmic reactions is that the reactions with CH_4 as a reference are more convenient for comparison with both **13a** and **13d** because all the four species of these equilibria have an sp^3 carbon. In contrast, for **13b** ethylene is a more convenient model since all four species in these reactions have an sp^2 carbon.

The hydroxyimine **13d** formally resembles the amide **13a** by having a double bond to an heteroatom and a single bond to a resonatively electron-donating heteroatom. It is therefore not surprising that the ΔH of eqs 4a and 5a or of 4b and 5b differ by only ca. 2 kcal/mol, accounting for the small substituent effect.

Structural Effects and K_{Enol} Values. The present data extend the scope of the enols of carboxanilides which we started to screen previously.[2] There is one new solid enol (**8**), and in solution we have the same multitude of

behavior. The enol is the observable major component in a tautomeric mixture (**8** in $CDCl_3$ at 220 K), it is the minor component of an amide/enol mixture (**9** in $CDCl_3$), it is in a rapid equilibrium with an isomeric species, (**12**, **14**, and perhaps **13**), and it is not observed and is much less favorable than an enol on a keto function (**10** and **11**). The number of known (i.e., observed as pure species or in an equilibrium mixture) enols of amides, activated by β-EWGs is now close to dozen and they cannot be regarded anymore as esoteric species.

The data are still mostly qualitative. The range of experimental K_{Enol} values is limited by the NMR techniques, sometimes by the lower solubility in nonpolar solvents where K_{Enol} is higher than in polar ones, by the several potential enolization sites which are not easily distinguishable when the enol is present in a small percentage, by the exchange of the enol with a tautomer which cannot be always frozen, and by the slow decomposition of some of the compounds in solution.

In the present work, for ethyl anilidonitroacetate **9** $0.09 > K_{Enol} > 0.05$ in $CDCl_3$ provided that the minor species is indeed **9b**. For methyl anilidocyanoacetate **8**, K_{Enol} in $CDCl_3$, at 220K, where an OH was observed is ≥ 9. The percentage of enol (i.e., K_{Enol} values in $CDCl_3$) derived from the varied data for YY′CHCONHPh is qualitatively in the following order of YY′: *c*-$(RCO_2C)_2$ [meldrum acid] > NC, CO_2Me > NC, NC ≫ CO_2Me, CO_2Me ∼ NO_2, CO_2Me.

Qualitatively, the percentage of enol for **8** and **9**, as well as for **5** and **6**, is lower in DMSO-d_6 or CD_3CN than in $CDCl_3$, CCl_4 or $Cl_2CDCDCl_2$. This is explained by the higher polarity of the amide form, which is more favored in the more polar solvent.

Experimental Section

General Methods. Melting points, FT IR spectra, NMR spectra and low- and high-resolution mass spectra were recorded as described previously.[4b]

Solvents and Materials. The active methylene compound, phenyl isocyanate, and commercial deuterated solvents ($CDCl_3$, DMSO-d_6, CD_3CN) were purchased from Aldrich and were used without further purification.

Reaction of Methyl Cyanoacetate with Phenyl Isocyanate. (a) A mixture containing methyl cyanoacetate (1 g, 10.1 mmol), phenyl isocyanate (1.0 mL, 10.1 mmol), and Et_3N (2.80 mL, 20.2 mmol) in dry DMF (7 mL) was stirred for 4 h at 60 °C and then for 16 h at room temperature. The mixture was poured into a cooled 2 N aqueous solution, extracted with EtOAc, washed with water, dried (Na_2SO_4), and evaporated. The crude solid was crystallized from EtOAc/petroleum ether, giving 1.14 g (52%) of **8** as a white solid, mp 144−145 °C. ^{1}H NMR ($CDCl_3$, rt) δ: 3.88 (3H, s, CO_2Me), 7.23−7.41 (5H, m, Ph), 7.88 (<1H, br, NH), 15.40 (<1H, OH, not always observed). On shaking with D_2O the signals at δ 7.88 and 15.40 disappeared. The spectra at 243 and 220 K are similar except for a minor shift and a sharper OH signal at δ 15.15. δ (DMSO-d_6, rt): 3.70 (3H, s, CO_2Me), 5.60 (ca. 1.5H, br, exchanging CH), 7.07 (1H, t, *p*-Ph-H), 7.31 (2H, t, *m*-Ph-H), 7.50 (2H, d, *o*-Ph-H), 10.68 (0.7H, br s, NH). The signals at δ 5.60 and 10.68 disappear on shaking with D_2O. ^{1}H NMR (CCl_4, with external C_6D_6, low solubility) δ: 3.03 (1H, CH), 4.83 (3H, CO_2Me), 8.11 (1H, *p*-Me), 8.28 (2H, Ph-H), 8.35 (2H, Ph-H), 9.43 (ca. 1H, NH), 16.25 (0.7H, OH). ^{1}H NMR (CD_3CN, rt) δ: 3.83 (3H, s, CO_2Me), 4.86 (ca. 0.5H, br s), 7.16−7.55 (5H, m, Ph), 8.30 (0.15H, br s), 8.85 (ca. 0.5H, br s). At 230 K the compound started to precipitate. The proton spectrum showed broad signals at δ 2.2, 3.7, 3.80 (3H, CO_2Me), 4.87 (small), 7.35 (5H, Ph), 8.50 (small) and 9.08 (small). At 340 K the number of signals is smaller. Except for the MeO and the 5-Ph-H signals the broad peaks at 4.88 and 8.68 remained and a broad signal at 3.77 overlaps the main MeO signal. ^{13}C NMR (uncoupled, $CDCl_3$) δ: 52.59 (CH_3, q), *57.74* (s, C_β), 116.22 (s, CN), *122.69* (d of d, C_m), 126.31 (d of d), 129.16 (d), *134.91* (m, C_{ipso}), *171.11* (C_α, d, J = 4.7), 173.75 (CO_2Me, m). Except for small shifts the same spectrum was obtained at 220 K. In the presence of a 1:1 D_2O/H_2O mixture the four *italicized* signals were split to 57.66 + 57.70; 122.63 + 122.74; 134.87 + 134.89; 170.90 + 170.99. ^{13}C NMR (DMSO-d_6, rt) δ: 52.71 (br, vw, sometimes unobserved), 119.66 (d of m, C_o), 123.90 (br), 128.85 (d of d, C_m), 138.05 (C_{ipso}), 164 (br, vw, sometimes unobserved). On adding a 1:1 D_2O/H_2O solution the signals at δ 123.90, 138.97 broadened. When heated for 30 min at 366.8 K signals were observed at δ 23.56, 25.96, 40.02, 52.18, 114.51, 119.21, 123.68, 128.19, 137.77, 160.22, 163.88. ^{13}C NMR (CD_3CN, coupled) δ: 46.76 (d, J = 136 Hz), 52.36 (d, J = 148 Hz), 53.96 (d, J = 148 Hz), 57.47 (s) [all small], 120.09 (d, J = 162 Hz), 124.17 (d, J = 163 Hz), 125.13 (d of t, J = 162 Hz), 126.58 (Ph), 129.02 (large, CN), 137.40 (m, C_{ipso}). Smaller signals are observed at δ ca. 158, 162.5, 171. At 340 K small signals at ca. 48, 53.91, 120.89 and 125.70 and an intense signal at 129.25 (CD_3CN) were observed. IR (ν_{max}, cm^{-1}, $CHCl_3$): 3193 (m, OH), 2218 (s, CN), 1642 (s, C=O). (b) When a mixture containing the ester (1 g, 10.1 mmol), PhNCO (1.65 mL, 15.14 mmol) and Et_3N (3.54 mL, 25.23 mmol) was heated at 50 °C for 3 h without a solvent and then worked up as above, 3.9 g of a crude solid was obtained. Column chromatography on silica gel gave two fractions. The first one, 0.92 g, mp 141−3 °C was identical with that described above except for the absence of a signal at 7.88. The second one (1.34 g) showed a complex NMR spectrum.

Microanalysis: Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.24; H, 4.69; N, 12.54.

Crystallographic Data: $C_{11}H_{10}N_2O_3$, space group $P2_1/n$; a = 22.561(5) Å, b = 5.856(1) Å, c = 8.048(2) Å; β = 93.66(2)°, V = 1061.1(8) Å^3, Z = 4, ρ_{calcd} = 1.37 g cm^{-3}, μ (Mo Kα) = 0.95 cm^{-1}, no. of unique reflections 2063, no. of reflections with $I \geq 3\sigma_I$ 1326, R = 0.059, R_w = 0.086.

Reaction of Ethyl Nitroacetate with Phenyl Isocyanate. A solution of ethyl nitroacetate (1 g, 7.5 mmol), phenyl isocyanate (0.81 mL, 7.5 mmol), and Et_3N (2.2 mL, 15 mmol) in DMF (7 mL) was heated with stirring for 4 h at 60 °C and then stirred for additional 16 h at room temperature. The mixture was poured into ice-cold 2 N aqueous HCl solution, the aqueous phase was extracted with EtOAc, the organic layer was washed with water and dried (Na_2SO_4), and the solvent was evaporated. The crude residue (1.74 g, 97%) was chromatographed over silica gel using a 1:4 EtOAc−petroleum ether eluent, giving 0.95 g (50%) of pure **9**, which after recrystallization from ether−petroleum ether has a mp of 98−9 °C.

^{1}H NMR ($CDCl_3$) δ: 1.38 (3H, t, J = 7.2 Hz, Me), 4.36−4.50 (2H, q, J = 7.2 Hz, CH_2), 5.91 (1H, s, CH), 7.23 (1H, t, *p*-Ph-H), 7.37 (2H, t, *m*-Ph-H), 7.56 (2H, d, *o*-Ph-H), 8.99 (ca. 1H, br s, NH). A weak singlet (<0.1H) was also observed at δ 16.66 and on shaking with D_2O it disappeared. At 243 and at 220 K there are four signals of 0.02−0.03H intensity at δ 19.32, 16.84, 12.03 and 11.94, a very broad small signal at δ 15.86, 1H signals at δ 9.51 and 6.10 and the Ph and Et signals. ^{1}H NMR (CCl_4, with external $(CD_3)_2CO$, low solubility) δ: 1.38 (3H, t, Me) signal), 4.36 (2H, t, CH_2), 7.10 (1H, t, *p*-H), 7.25 (2H, m, *m*-H), 7.49 (2H, t, *o*-H), 8.84 (1H, s, NH). ^{1}H (DMSO-d_6) δ: 1.24 (3H, t, J = 7.1 Hz, Me), 4.30 (2H, q, J = 7.1 Hz, CH_2), 6.57 (0.5H, s, CH **?**), 7.15 (1H, t, *p*-Ph-H), 7.42 (2H, t, *m*-Ph-H), 7.54 (2H, d, *o*-Ph-H), 10.77 (0.25H, br s, NH). ^{13}C NMR (uncoupled, $CDCl_3$) δ: 13.76 (q of t, Me), 64.73 (t of q, CH_2), 89.35 (d, CH), 120.48 (d of m, C_o), 125.84 (d of t, C_p), 129.22 (d of d, C_m), 136.08 (t, J = 7.5 Hz, C_{ipso}), 155.44 (d, J = 3.3 Hz, CONHPh), 161.84 (q, J = 3.3 Hz, CO_2Et). In the presence of a 1:1 D_2O/H_2O mixture the signals at δ 120.48 and 155.44 split to δ 120.38 + 120.48 and 155.42 + 155.54. At 220K all signals were somewhat shifted, and a few Hz to a lower field of most aromatic signals, signals of the same multiplicity having 3−4% of the intensities of the corresponding major signals had appeared. ^{13}C NMR (uncoupled, DMSO-d_6) δ: 13.60 (q, Me), 19.49 (d, J = 4 Hz), 63.13 (t, CH_2), 89.83 (d,

CH), 119.46 (d of m, C_m), 124.68 (d of t, C_p), 129.01 (d of d, C_o), 137.45 (t, J = 10 Hz, C_{ipso}), 156.75 (d of d, J = 5, 1.7 Hz, CONHPh), 160.94 (2 overlapping t, J = 3.3 Hz, CO_2Et). IR (ν_{max}, cm^{-1}, $CHCl_3$): 3326 (s), 3214 (m), 3158 (m), 3108 (m), 1754 (s, C═O), 1677 (s, C═O).

Microanalysis: Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.79; N, 11.10. Found: C, 52.78; H, 4.83; N, 10.90.

Reaction of Malononitrile with Phenyl Isocyanate. This reaction was conducted several times under different conditions: (a) A mixture of malononitrile (1 g, 15.15 mmol), phenyl isocyanate (1.64 mL, 15.15 mmol), and Et_3N (5 mL, 36.07 mmol) in dry DMF (7 mL) was heated at 70 °C for 30 min and then stirred at room temperature for 20 h. It was poured into 2 N aqueous HCl, and the solid obtained was filtered, washed with water, dried, and crystallized from EtOAc/CH_2Cl_2, giving 1.85 g (66%) of solid **12**, mp 168−170 °C (sublimed). ^{1}H NMR ($CDCl_3$) δ: 7.26−7.55 (5H, m, Ph), 8.06 (1H, br s, NH); ^{1}H (DMSO-d_6) δ: 6.26 (2H, v br, not always observed), 6.85 (1H, t, *p*-Ph-H), 7.15 (2H, t, *m*-Ph-H), 7.48 (2H, d, *o*-Ph-H), 8.02 (∼0.1H, very b, NH). ^{13}C NMR (uncoupled, DMSO-d_6) δ: 34.38 (s), 120.06 (d of q, C_o or C_m), 121.01 (s, CN), 122.24 (d of t, C_p), 128.35 (d of m, C_o or C_m), 139.61 (d, J = 9 Hz, C_{ipso}), 167.61 (s). On shaking the solution with 1:1 D_2O/H_2O the signal at 122.24 is split to two very close signals. ^{1}H NMR (CD_3CN, rt) δ: 5.15 (0.8H, br, CH), 7.20 (1H, t, *p*-H), 7.41 (2H, t, *m*-H), 7.49 (2H, d, *o*-H), 8.82 (1H, s, NH). At 233K the two broad signals (now at δ 5.22 and 9.05) sharpen and each integrates to 0.8−0.9H. When D_2O (0.6 mL) was added to the solution (10 mg) in CD_3CN (0.5 mL) at room temperature, the signals at δ 5.15 and 8.82 were absent immediately after mixing. In another experiment without D_2O at room temperature, small signals at δ 2.09 and 2.20 (br) were observed on dissolution, but their intensities increase on standing and after 5−9 days they were the major signals. We ascribe this behavior to decomposition of **12**. IR ($\nu_{max:}$, cm^{-1}, $CHCl_3$): 3467 (vw, OH), 3242 (m, OH), 2232 (m, CN), 2204 (s, CN), 1642 (m, C═O). IR ($\nu_{max:}$, cm^{-1}, Nujol): 3432 (vw), 3242 (w), 2239 (m, CN), 2197 (s, CN), 1712 (s), 1635 (s).

Microanalysis: Calcd for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.62; H, 4.01; N, 22.44

(b) Malononitrile (1 g, 15.2 mmol), phenyl isocyanate (2.74 g, 22.7 mmol), and Et_3N (5.3 mL, 37.9 mmol) were kept without a solvent at 58 °C for 130 min. The complex mixture (by TLC and NMR) obtained was purified by column chromatography over silica gel using 25% EtOAc/petroleum ether as eluent. One fraction (1.10 g) displayed the following ^{1}H NMR ($CDCl_3$) δ: 7.11−7.59 (H, m, Ph), 8.93 (1H, br s), which was not changed on shaking with D_2O. (c) Malononitrile (1 g, 15.2 mmol), PhNCO (3.6 g, 30.3 mmol) and Et_3N (7.44 mL, 53 mmol) were heated for 4 h at 88 °C. Chromatography gave a mixture and one fraction which was eluted with 30−35% CH_2Cl_2/petroleum ether (1.31 g) has a mp of 206−236 °C and is probably crude N,N′-diphenylurea, mp 238 °C. ^{1}H NMR ($CDCl_3$) δ: 7.14−7.49 (H, m, Ph).

Microanalysis: Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.07; H, 5.55; N, 12.59.

Reaction of Malononitrile with Potassium Cyanate. This is a modification of the literature method.[14] To a solution of malononitrile (4 g, 60.61 mmol) in DMF (30 mL) was slowly added finely powdered potassium cyanate (4.91 g, 60.61 mmol) with vigorous stirring during 1 h. The mixture was refluxed with stirring for 1 h, cooled to room temperature, and diluted with ether (50 mL), and the solid formed was filtered and washed with water, giving the pure yellowish potassium salt (8.4 g, 94%), mp 276−278 °C (with decomposition). IR (Nujol, ν_{max}, cm^{-1}): 3472 (m), 3311 (m), 3201 (m), 2204 (s), 2182 (s), 1661 (s), 1588 (s).

Anal. Calcd for $C_4H_2N_3OK$: C, 32.7; H, 1.5; N, 28.6. Found: C, 32.86; H, 1.43; N, 28.90%.

The salt was converted to carbamoyldicyanomethane, a gray-white solid, mp >300 °C dec in 94% yield, by exchange on an ion exchange (Amberlite IR 120(H)) resin.[14] ^{1}H NMR (DMSO-d_6) δ: 5.58 or 7.94 (br s) and very small signals at 2.71, 2.94. ^{13}C NMR (coupled, DMSO-d_6, rt) δ: 34.65 (s, C_β), 117.87 (s, CN), 172.69 (s, C_α). IR (Nujol, ν_{max}, cm^{-1}): 3582 (m), 3499 (s), 3428 (s), 3326 (s), 3216 (s), 2800−2400 (br, including peak at 2629), 2233 (s, CN), 2203 (s, CN), 1654 (s). HRMS: 127.0373 (94), 109.0289 (47), calcd for $C_4H_5N_3O_2$ 127.0382, for $C_4H_3N_3O$ 109.088.

Anal. Calcd for $C_4H_3N_3O$: C, 44.05; H, 2.77; N, 38.52. Found: C, 42.40; H, 3.00; N, 37.85%.

Reaction of Methyl Propanoyl Acetate with Phenyl Isocyanate. To a stirred solution of methyl propanoyl acetate (2 g, 15.36 mmol) and Et_3N (4.26 mL, 30.74 mmol) in DMF (16 mL) was added phenyl isocyanate (1.68 mL, 15.36 mmol) with stirring. Workup was identical with that described below for the reaction of ethyl acetoacetate, and the crude product (3.5 g, 92%) was crystallized from petroleum ether (40−60 °C), giving **10** as a white solid (2.4 g, 63%), mp 40−41 °C. ^{1}H NMR ($CDCl_3$) δ: 1.22 (3H, t, J = 7.5 Hz, Me), 2.84 (2H, q, J = 7.5 Hz, CH_2), 3.83 (3H, s, Me), 7.15 (1H, t, J = 7.5 Hz, *p*-H), 7.35 (2H, t, J = 8.1 Hz, *m*-H), 7.53 (1H, d, J = 7.8 Hz, *o*-H), 11.22 (0.9H, s, NH), 18.34 (1H, s, OH). On addition of D_2O the signal at δ 18.34 disappears almost completely after a short time. ^{13}C NMR ($CDCl_3$) δ: 10.61 (q of t, J = 129 Hz, J = 5.0 Hz, CH_2*Me*), 31.57 (t of quintets, ^1J = 131 Hz, J = 4.5 Hz, CH_2), 51.50 (q, J = 147 Hz, MeO), 94.04 (5 lines m, J = 4.2 Hz, C_β), 121.41 (d of m, ^1J = 163 Hz, C_o), 124.76 (d of t, ^1J = 162 Hz, J = 7.5 Hz, C_p), 128.90 (d of d, ^1J = 162 Hz, ^2J = 8.4 Hz, C_m), 136.90 (t of m, C_{ipso}), 169.59 (d, J = 4 Hz, C_α or CONH), 170.97 (s, CO_2Me), 196.19 (quintet, J = 5.0 Hz, C═O). After shaking with D_2O, the lowest field signal is unsymmetrical quintet at δ 194.91, C_α is an unsymmetrical q, and the quintet at 31.57 is now a quartet at δ 31.24.

A long-range C−H correlation exists between the OH and CH_2, with C_β, and with the δ 170, 196.19 signals. IR (Nujol, ν_{max}, cm^{-1}): 3194 (w), 2900−2500 (H bonded OH), 1676 (CO); IR ($CHCl_3$): 3238 (m), 3194 (m), 2886, 1668 (CO).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.56; H, 6.10; N, 5.32%.

Reaction of Ethyl Acetoacetate with Phenyl Isocyanate. To a stirred solution containing ethyl acetoacetate (2 g, 15.4 mmol) and Et_3N (4.26 mL, 30.7 mmol) in DMF (14 mL) was added phenyl isocyanate (1.68 mL, 15.4 mmol), and stirring was continued for 1 h at room temperature and then for 45 min at 40−45 °C. The mixture was cooled to room temperature, poured into a cold 13% solution of aqueous HCl and extracted with EtOAc. The organic phase was washed with water (50 mL), dried (Na_2SO_4), and the solvent was removed yielding a solid (4 g, ca. 100%). Crystallization from petroleum ether (40−60 °C) gave **11** as a white solid (2.83 g, 74%), mp 57−8 °C. ^{1}H NMR ($CDCl_3$, 223 K [and room temperature]) δ: 1.31 [1.33] (3H, t, J = 6.9 Hz, Me) 2.17 (≤0.1 H, small s), 2.42 [2.48] (3H, s, Me), 4.17 [4.31] (2H, t, CH_2, J = 6.6 Hz), 7.13 [7.14] (1H, t, J = 7.2 Hz, *p*-Ph-H), 7.34 [7.35] (2H, t, J = 7.8 Hz, *m*-Ph-H), 7.53 [7.53] (2H, d, J = 8.4 Hz, *o*-Ph-H), 11.49 [11.28] (1H, s, NH), 18.43 [18.17] (1H, s, OH). On shaking with D_2O at room temperature the signal at 18.17 ppm disappears. ^{13}C NMR ($CDCl_3$, coupled, 223K [rt]) δ: 13.80 [14.07] (q of t, J = 130 Hz), 26.79 [26.17] (q of d, J = 130 Hz, J = 5.1 Hz), 60.81 [60.70] (t of q, J = 148 Hz, J = 4.5 Hz), 94.19 [94.86] (m), 120.66 [121.11] (d of br m), 124.34 [124.53] (d of t J = 163 Hz, J = 7.5 Hz), 128.64 [128.75] (d of d, J = 162 Hz, J = 8 Hz), 136.34 [136.88] (t of m), 168.81 [168.94] (br, s), 170.30 [170.69] (s), 192.26 [191.88] (quintet, J = 6 Hz). In D_2O the δ 26.79 signal is a q of s and the 168.81 signal is a t and δ 190.72 is a q + s. IR ($CHCl_3$, ν_{max}, cm^{-1}): 3238 (m, O−H), 3000−2830 (m, O−H), 1720 (m), 1668 (C═O, s). IR (Nujol): 3157 (m), 1720 (m), 1685 (s).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.84; H, 6.12; N, 5.45%.

Crystallographic Data. 11: $C_{13}H_{15}NO_4$, space group $P2_1/n$; a = 14.349(3) Å, b = 14.107(3) Å, c = 6.319(1) Å; β = 98.83-(2)°, V = 1263.9(7) Å^3, Z = 4, ρ_{calcd} = 1.31 g cm^{-3}, μ (Mo Kα) = 0.98 cm^{-1}, no. of unique reflections 3813, no. of reflections with $I \geq 3\sigma_I$, R = 0.067, R_w = 0.093.

Reaction of Barbituric Acid with Phenyl Isocyanate. To a solution of barbituric acid (1 g, 7.8 mmol) in dry DMF (8 mL) was added Et_3N (2.16 mL, 15.6 mmol), and after the solution was stirred for 5 min phenyl isocyanate (0.85 mL, 7.8

mmol) was added and the reaction mixture was stirred for 90 min at room temperature. The mixture was poured into ice-cold 1:9 concentrated HCl/H_2O mixture, the crude solid obtained was filtered and washed with H_2O, and the wet solid was heated with 1:4 EtOAc/petroleum ether (40−60 °C) (50 mL) and filtered, giving **14** as a white solid (1.45 g, 75%), mp 292−96 °C dec.

^{1}H NMR (DMSO-d_6) δ: 7.20 (1H, t, *p*-Ph-H), 7.42 (2H, t, *m*-Ph-H), 7.51 (2H, d, *o*-Ph-H), 11.51 (1H, s, NH), 11.96 (vw, v br, NH). There are additional overlapping small signals (<0.07 H) in the Ph region at 7.45, 7.26 (t) and 6.94 (t) ppm. The signals at δ 11.51 and 11.96 disappear on shaking the solution with D_2O. ^{13}C NMR (DMSO-d_6, coupled) δ: 80.26 (C_α, narrow m), 117.97, 120.93 (both small, with intensity 5−6% of main signal), 121.06 (d of m, J = 163 Hz), 125.11 (d of t, J = 163 Hz), 128.62 (small, intensity 7% of the main signal), 129.08 (d of d, J = 162, J = 8 Hz, most intense signal), 135.80 (t, J = 6 Hz, C_{ipso}), 148.47, 168.70 (NHCO). IR (Nujol, ν_{max}, cm^{-1}): 3282 (w, OH), 3252 (w, OH), 3157 (w), 2365 (w), 1808 (w), 1764 (s), 1690 (s, C═O), 1639. HRMS: calcd for $C_{11}H_9N_3O_4$ 247.212, found 247.0605 (rel abundance (18%): base peak 93.0585, calcd for $PhNH_2^+$ 93.1293.

Anal. Calcd for $C_{11}H_9N_3O_4$: C, 53.45; H, 3.67; N, 16.99. Found: C, 53.36; H, 3.92; N, 16.77%.

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Supporting Information Available: Tables S1−S8 of general X-ray data, bond lengths and angles, and position and thermal parameters, and Table S9 of energies of the species used in the calculations and Figures S1 and S2 of stereoviews of **8** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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