

# *N*-Isopropyl enols of carboxylic acid amides<sup>†</sup>

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**ABSTRACT:** Eight *N*-isopropyl compounds of the formal structure  $YY'CHCONHPr-i$  (**6**),  $Y, Y' = CO_2Me, CO_2CH_2CF_3, CN$ ;  $YY' =$  Meldrum's acid residue;  $Y = CO_2Me, Y' = CO_2CH_2CF_3, CN$ ;  $Y = CO_2CH_2CF_3, CO_2CH(CF_3)_2, Y' = CN$ , and the *N*-*t*-butyl derivative of Meldrum's acid were prepared and their structures were investigated in the solid state and in solution. The x-ray diffraction data indicate that in the solid state the structure is that of the amide **6**, when  $Y = Y' = CO_2Me$ , whereas when  $Y = CO_2Me, Y' = CN$  or  $YY' =$  Meldrum's acid residue the structure is that of the enol (**5**)  $YY'C=C(OH)NHPr-i$ . The solid-state <sup>13</sup>C spectra indicate structure **6** when  $Y = CO_2Me, Y' = CO_2R, R = Me, CH_2CF_3$  and an enol structure for the other compounds studied. <sup>1</sup>H, <sup>13</sup>C and when available <sup>19</sup>F NMR spectra showed that the enol/amide composition in solution is structure and solvent dependent, in analogy with the previously investigated *N*-Ph analogs. The percentage of enol (and  $K_{Enol}$ ) decrease in the order of solvents  $CCl_4 > CDCl_3 > THF-d_8 > CD_3CN > DMSO-d_6, DMF-d_7$ . For  $Y, Y'$  the percentage of enol increases when the number of fluorine atoms in R of the  $CO_2R$  increases, when CN replaces a  $CO_2R$  group or for the cyclic Meldrum's acid derivative. Both *E*- and *Z*-enols were observed when  $Y \neq Y'$ , mostly at low temperature. The  $\delta(OH)$  values increase with increased polarity of the medium and with increased strength of the hydrogen bonds in which they are involved. In  $THF-d_8$  and  $DMF-d_7$  the *Z*-enol/*E*-enol and the amide/enol ratios increase with increase in temperature. A main conclusion from the work is that the percentage of the enol increases, but not drastically, when the *N*-substituent is changed from Ph to *i*-Pr. Copyright © 2003 John Wiley & Sons, Ltd.

**KEYWORDS:** carboxylic acid amides; *N*-isopropyl enols

## INTRODUCTION

Enols of carboxylic acid amides are still not common species in non-heterocyclic systems,<sup>1</sup> although a few of them had been observed as short-lived intermediates.<sup>2</sup> We recently obtained a fair number of them as stable isolable species by substituting simple carboxylic acid amides by two  $\beta$ -electron-withdrawing groups (EWGs)  $Y, Y'$ .<sup>3</sup> The rationale behind it is that the low stability of the enols **2** compared with the tautomeric amides **1** is due to resonative electron donation by the NHR group as shown by resonance structure **1a**. We reasoned that a similar resonative electron donation would have stabilized the enols **2** if resonatively EWGs will delocalize the negative charge in resonance structure **2a** [Eqn. (1)].<sup>3</sup> This approach had led to the observation of *N*-phenyl-substituted enols **3a–c** carrying two ester groups in a mixture with the amides **4a–c** in solution and of **3c** in the

solid, whereas **4a** and **4b** are the structures in the solid.<sup>3a,c</sup> The  $\beta$ -CN,  $\beta$ -COOR systems **3d–f** and the Meldrum's acid derivative **3h** are all enolic in the solid and exclusively enols or enol–amide mixtures in solution.<sup>3d</sup>

Consequently, electronic changes of the  $\beta$ -substituents affect the enol–amide equilibria [measured by  $K_{Enol}$  of Eqn. (1)] and solvent effects had also shown a consistent decrease of the percentage of the enol from  $CCl_4, CDCl_3$  and THF to the polar solvents  $CD_3CN$  and DMSO.<sup>3</sup> These two parameters cause small to major changes in the solid state structure and in  $K_{Enol}$  values in solution.

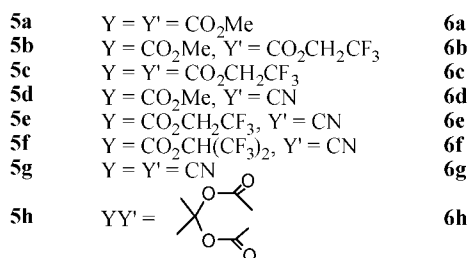
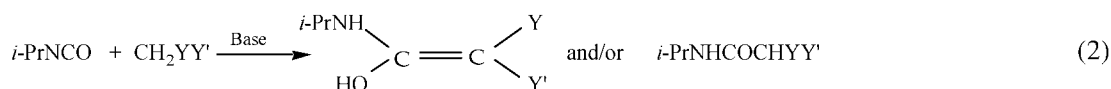
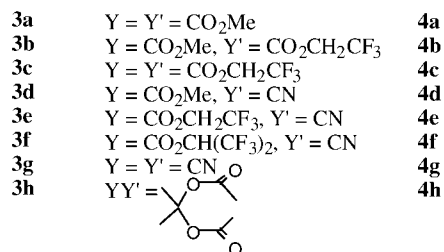
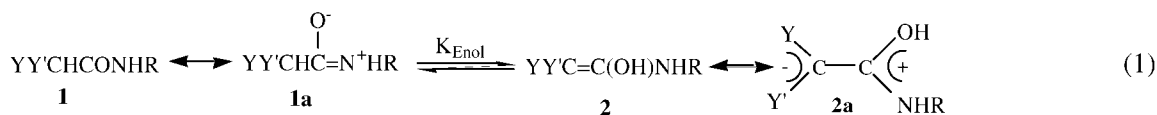
We are interested in the ability for fine tuning of the enol/amide ratios and an additional parameter is the substituent on the nitrogen. In a previous study, the effect of replacing the *N*-Ph group by an *N*-substituted [*p*-Me, *p*-MeO, *p*-Br, 2,4-(MeO)<sub>2</sub>] phenyl group led to minor changes in  $K_{Enol}$  for systems **3b** and **3c** and to a regular change for systems **3e** and **3f** in  $CD_3CN$ .<sup>3c,d</sup> However, a much larger variety is anticipated by using *N*-alkyl substituents. Nothing is known about the effect of the change *N*-Ar  $\rightarrow$  *N*-alkyl on the enol–amide equilibria and we report here on the preparation and study of the *N*-*i*-Pr enols analogs of systems **3a–h** and the *N*-*t*-butyl analog of **3h**.

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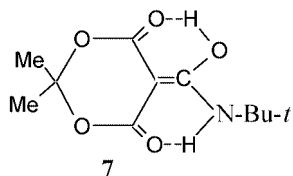
## RESULTS

### Synthesis

Reaction of isopropyl isocyanate with methylene compounds CH<sub>2</sub>YY' substituted by EWGs Y,Y' in the presence of base gave eight compounds with the formal structures *i*-PrNHCOCHYY', which can be either the enols **5a–h** or the amides **6a–h** [Eqn. (2)]. The *N*-*t*-Bu analog of **5h**, i.e. **7**, was also prepared but similar reactions when Y = Y' = CO<sub>2</sub>Me or CO<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub> and Y = CO<sub>2</sub>Me, Y' = CO<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub> failed.

### Structure determination

The previous studies<sup>3</sup> showed that systems which exist either as the enol or the amide in the solid state can still give enol–amide mixtures in solution. Consequently,



systems **5a/6a–5h/6h**, **7** were investigated both in the solid state and in solution.

### Solid-state structures

**X-ray diffraction.** The solid-state structures of three representatives of the two main systems, i.e. **5** (enol) and **6** (amide) were determined. The compounds were **5a/6a**, **5d/6d** and **5h/6h** whose *N*-Ph analogs were shown previously by x-ray diffraction to have structures **4a**, **3d** and **3h**, respectively. The *N*-isopropyl analogs display analogous structures. A single crystal of the (CO<sub>2</sub>Me)<sub>2</sub> compound, crystallized from EtOAc–petroleum ether, showed the amide structure **6a**, as shown by the ORTEP drawing in Fig. 1 (the stereoview has been deposited in the Cambridge Structural Database). There are three independent molecules in the unit cell. One molecule displays a hydrogen-bonded homopolymeric network, where O(1) is hydrogen-bonded to the NH of a second molecule, whose O(1) is hydrogen-bonded in turn to the NH of a third molecule. The two other types of molecules form a similar heteropolymer array, with a repeated second molecule–third molecule hydrogen-bonded unit. Selected bond lengths and angles are given in Table 1.

The crystallographic data for **6a** are as expected for an

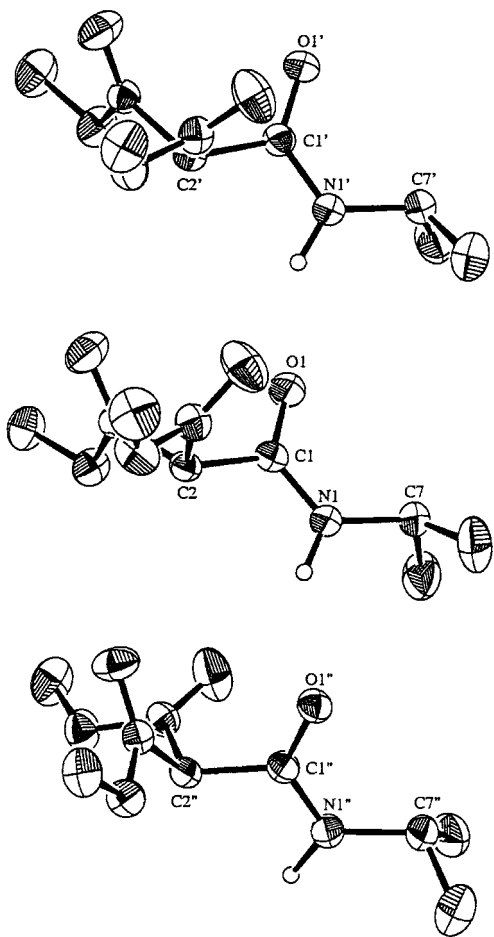


Figure 1. Structure of **6a** in the crystal (ORTEP drawing)

amide. The C(1)C(2) bond length of 1.530 Å (1.531 Å for the other molecules) and the C(1)N(1) bond of 1.322–1.328 Å are normal for C—C and C—N single bonds, whereas the C(1)O(1) and C(3)O(2) distances of 1.223–1.235 and 1.177–1.192 Å, respectively, are characteristic for a C=O bond of a C(=O)X moiety.

In contrast, the structure of the (cyano) methoxycarbonyl system is that of the enol **5d**, with a 'dimeric' structure in which two molecules are doubly hydrogen-bonded. The amido nitrogen of one molecule is hydrogen-bonded to the cyano nitrogen of a second molecule and the same applies to the other *i*-Pr—N—H...NC moiety. The ORTEP drawing is in Fig. 2 (the stereoview has been deposited in the Cambridge Structural Database) and selected bond lengths and angles are given in Table 1.

Likewise, the Meldrum's acid derivative has the enol structure **5h**. The ORTEP drawing is shown in Fig. 3 (the stereoview has been deposited in the Cambridge Structural Database) and selected bond lengths and angles are given in Table 1.

The structure found for **5d** is characteristic of enols of amides having push–pull substituents.<sup>3</sup> The C(1)C(2) bond at 1.415 Å is very long for a C=C bond, reflecting

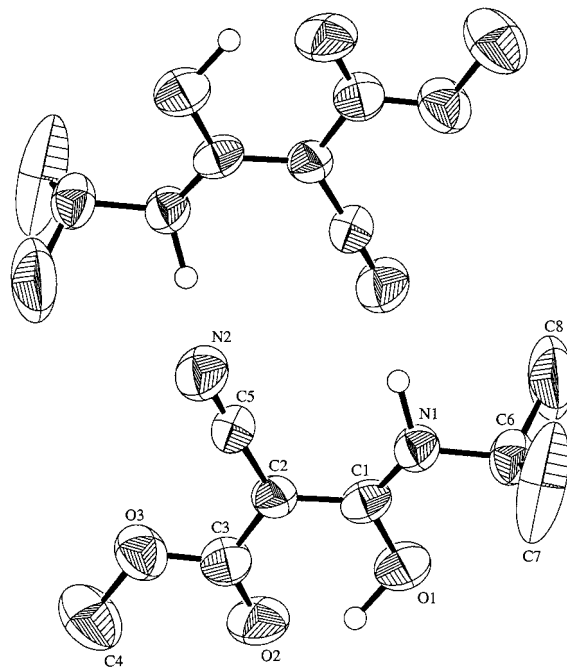


Figure 2. Structure of **5d** in the crystal (ORTEP drawing)

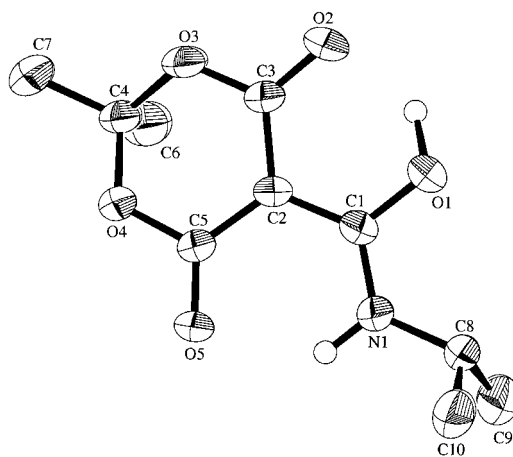


Figure 3. Structure of **5h** in the crystal (ORTEP drawing)

the contribution of the zwitterionic hybrid **2a** and the C(1)O(1) bond of 1.318 Å is a single bond. The angles around the C(1)C(2) bond are close to the C(sp<sup>2</sup>)—C(sp<sup>2</sup>) bond angle being 117.1–124.6°. The O—H is *cis* to the ester group with an O(1)O(2) non-bonding distance of 2.471 Å, indicating a strong hydrogen bond. This bond is asymmetric with O(1)H and O(2)...H distances differing by 0.45 Å, and non-linear with an O(1)HO(2) angle of 135°. The intermolecular non-bonding N(1)N(2) distance is 3.03 Å and the NHN hydrogen bond is long, very asymmetric and bent [N(1)H 1.10 Å, N(2')...H(N1') 2.06 Å, N(2')HN(1) 145.5°].

The structure of **5h** resembles that of **5d** with even longer C(1)C(2) bond of 1.426 Å. The hydrogen bond is more asymmetric than that of **5d**:  $d(\text{O}\cdots\text{H}) - d(\text{O}-\text{H}) = 0.63$  Å; the OHO angle is 126°.

**Table 1.** Selected bond lengths and angles for **5d**, **6a** and **5h**

Bond	Length (Å)		
	<b>5d</b>	<b>6a<sup>a</sup></b>	<b>5h</b>
C(1)C(2)	1.415 (9)	1.530 (4) (1.531 (4)) [1.531 (4)]	1.426 (5)
C(1)O(1)	1.318 (7)	1.235 (4) (1.221 (3)) [1.223 (3)]	1.323 (5)
C(1)N(1)	1.293 (8)	1.322 (4) (1.328 (4)) [1.323 (4)]	1.327 (5)
C(2)C(3)	1.438 (9)		1.436 (5)
C(2)C(5)	1.412 (9)		1.427 (5)
C(3)O(2)	1.216 (8)	1.191 (4) (1.177 (4)) [1.192 (4)]	1.249 (5)
C(3)O(3)	1.328 (8)	1.300 (4) (1.323 (4)) [1.312 (4)]	1.324 (5)
C(4)O(3)	1.454 (9)	1.464 (5) (1.459 (5)) [1.454 (4)]	1.451 (5)
C(6)N(1)	1.468 (9)		
C(8)N(1)			1.477 (5)
C(7)N(1)		1.473 (4) (1.467 (4)) [1.467 (4)]	
C(5)N(2)	1.141 (8)		
O(1)H	1.11		1.07
O(2)···H	1.56		1.70
O(1)O(2)	2.471 (7)		2.48
O(1)O(5)		3.28	
N(1)O(2)		3.49	
N(1)O(5)			2.77
N(1)N(2') <sup>b</sup>	3.030 (8)		
N(1)H	1.10		0.96
N(2)···H(N1')	2.06		
O(5)···HN(1)			2.04
N(2')···H <sup>b</sup>	2.06		
O(1)N(1') <sup>b</sup>		2.951 (3)	
O(1')N(1'') <sup>b</sup>		2.966 (3)	

Bond angle	Angle (°)		
	<b>5d</b>	<b>6a<sup>a</sup></b>	<b>5h</b>
O(1)C(1)N(1)	117.1 (7)	124.7 (3) (124.4 (3)) [125.1 (3)]	116.1 (3)
O(1)C(1)C(2)	118.2 (7)	119.8 (3) (120.8 (3)) [120.1 (3)]	120.0 (3)
N(1)C(1)C(2)	124.6 (6)	115.4 (3) (114.7 (3)) [114.8 (2)]	123.9 (4)
C(3)C(2)C(5)	121.5 (7)	108.3 (2) (108.4 (2)) [109.6 (2)]	119.8 (3)
C(1)C(2)C(3)	118.7 (6)	108.9 (2) (107.8 (2)) [110.0 (2)]	117.4 (4)
C(1)C(2)C(5)	119.8 (6)	108.7 (2) (109.8 (2)) [109.0 (2)]	122.5 (3)
C(1)N(1)C(6)	122.8 (6)		
N(1'')C(7'')C(9'')		109.3 (3)	
C(8'')C(7'')C(9'')		111.6 (3)	
O(1)HO(2)	135.0		126.0
C(5)N(2)H(N1')	159.1		
N(2')HN(1)	145.5		
N(1)HO(5)			131.3

<sup>a</sup> Values for the two other crystallographically different molecules {(')} are in brackets.

<sup>b</sup> Intermolecular bond length.

Some parameters differ in the corresponding *N*-*i*-Pr and *N*-Ph derivatives but the data are limited and comparison is premature.

**Solid-state <sup>13</sup>C NMR spectra.** The x-ray structures discussed above indicate that the **5a/6a** system with no fluorine atoms in the ester group exists in the solid as the amide, **6a**. The replacement of one CO<sub>2</sub>Me by a CN leads to the solid enol, **5d**. Based on previous studies on systems **3/4** and analogies with the structures in solution<sup>3</sup> (the stereoviews have been deposited in the Cambridge Structural Database), it is expected that the cyanoester

systems with three or six fluorine atoms in the ester group, the dicyano, the bis(trifluoroethoxycarbonyl) or the Meldrum's acid substituted systems **5c-h** and **7** will also be enolic in the solid, whereas for system **5b/6b** with only three fluorine atoms prediction of the structure in the solid is uncertain. In the absence of x-ray data, <sup>13</sup>C NMR solid-state CP/MAS spectra easily supply the answer.

The solid-state <sup>13</sup>C CP/MAS spectral data for the six compounds studied are given in Table 2, from which it is clearly seen that **5a/6a** and **5b/6b** resemble each other, but differ from the other *N*-*i*-Pr derivatives investigated. In addition, the <sup>13</sup>C CP/MAS spectra show different shifts

**Table 2.** Solid-state  $^{13}\text{C}$  CP/MAS  $\delta$  values (in ppm) for **5/6**<sup>a</sup>

Compounds	$C_\alpha$	$C_\beta$	Y	Y'	<i>i</i> -Pr			CP-NQS	Assignment
					Me	H	$\Delta_{\alpha\beta}^c$		
<b>5a/6a</b>	164.5	58.5	166.3 53.3	166.3 53.3	22.8	42.6	106.0	CH	<b>6a</b>
<b>5b/6b</b>	162.4 162.8	58.2	164.8 51.6	166.8 61.4 125.3	22.5	42.8	104.2 104.6	CH	<b>6b</b>
<b>5c/6c</b>	169.1 <sup>b</sup>	71.7	166.8 61.2 124.5	172.5 61.2 124.5	20.8 22.0	44.1	97.4	quart	<b>5c</b>
<b>5d/6d</b>	171.1 <sup>b</sup>	55.8	171.1 52.6	116.7	21.9 22.9	43.7	115.3	quart	<b>5d</b>
<b>5e/6e</b>	172.4 <sup>c</sup>	56.3	172.4 61.2 124.3	117.9	19.5 23.3	45.8	116.1	quart	<b>5e</b>
<b>5g/6g</b>	170.9 176.7 <sup>d</sup>	36.1	117.2	117.2	22.0 23.3	44.4	134.8 140.6	quart	<b>5g</b>

<sup>a</sup> In **5** Y is *cis* to the OH. Of the several values for Y, Y', in the ester groups the first number is for COO, the second number for CH<sub>2</sub> (q) or Me (q) and the third one for CF<sub>3</sub> (t).

<sup>b</sup> In the broad peak at 171.1 peaks can also be identified at 172.1, 170.0 and 167.9 ppm that are not assigned.

<sup>c</sup> There are also minor peaks at 171.0, 168.8 and 166.5 ppm.

<sup>d</sup> There are also minor peaks at 169.8 and 174.7 ppm.

<sup>e</sup>  $\Delta_{\alpha\beta} = \delta C_\alpha - \delta C_\beta$ .

for the signals of the enol and amide forms, and of these only  $C_\alpha$  was taken into account because the shift difference was the most pronounced. For **5a/6a** and **5b/6b** the signals of  $C_\alpha$  are at 164.5 and 162.8 ppm, respectively, which are in the range of the  $C_\alpha$  values found in solution for the amides as summarized in Table 5.

In contrast, the  $C_\alpha$  chemical shifts for **5c/6c–5g/6g** range from 169.1 to 170.9 ppm, which agree with the  $\delta$  values found in solution for the  $C_\alpha$  of the enol form. A further parameter showing the difference between the amide and enol forms comes from the shift difference ( $\Delta_{\alpha\beta} = \delta C_\alpha - \delta C_\beta$ ) existing between  $C_\alpha$  and  $C_\beta$  (the carbon atoms attached to the O and the Y, Y', respectively). For **5a/6a**, **5b/6b** the observed  $\Delta_{\alpha\beta} = 104$ – $106$  ppm whereas for **5c/6c–5g/6g**  $\Delta_{\alpha\beta} = 115$ – $130$  ppm.

However, the  $\Delta_{\alpha\beta}$  values, taken alone, are not unequivocal for the structure assignment owing to possible strong substituent effects on  $C_\alpha$ . Thus, all the assignments were supported by cross-polarization non-quaternary suppression (CP-NQS)<sup>4,5</sup> experiments that are able to identify unequivocally quaternary carbons.

The CP-NQS experiments always completely cancel, for all the derivatives examined, the NCH CP/MAS signal at 42–46 ppm, but the  $C_\beta\text{HYY}'$  at 58.5 and 58.2 ppm only for **5a/6a** and **5b/6b**. In contrast, for **5c/6c–5g/6g** the CP/MAS signals in the range 36–72 ppm are fully detected in the CP-NQS spectra.

In conclusion,  $^{13}\text{C}$  NMR CP/MAS and CP-NQS unambiguously assigned the structures of **6a**, **6b** (amide) and **5c–g** (enol) to the *N*-*i*-Pr compounds. This corroborates the available x-ray diffraction data for **6a**, **5d** and **5h**.

## Excluding Other Structures

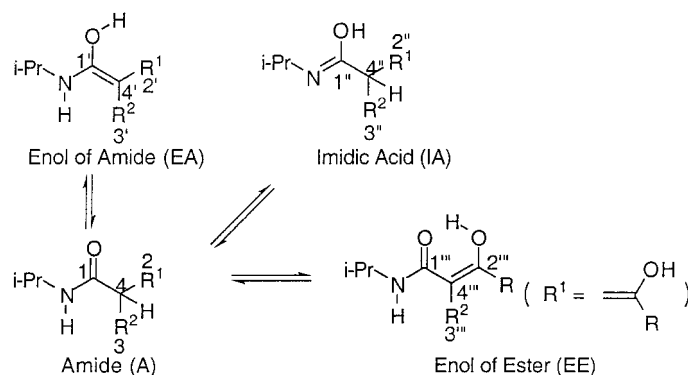
Owing to the presence of the enolic NH group and the ester group(s), an imidic acid (IA) and an enol of the ester (EE) isomers could also be in equilibrium with the amide (A) and enol of amide (EA) isomers. Although enols of

esters are known<sup>6</sup> in the many amides having Y and/or Y' = CO<sub>2</sub>R groups that we have studied so far, enolization is invariably on the amide group. To probe this question further we estimated the approximate chemical shifts of  $C_\alpha$ ,  $C_\beta$ , COO and CN for the four isomers by the ACD-LAB additivity scheme and compared the values with the observed solid-state shifts. The structures and the  $\delta$  and  $\Delta C_{\alpha\beta}$  values are given in Table 3. The IA structure is excluded since the calculated  $C_\alpha$  and  $C_\beta$  shifts are too low and too high, respectively, compared with the experimental values. The EE structure is excluded owing to the too low calculated  $C_\alpha$  and several too high  $C_\beta$  values.

## Structure in solution

The structures of the various systems in solution are substrate, solvent and temperature dependent. Owing to this, to broadening of signals for several systems and to possible ionization in the high-dielectric media, each system should be described separately.  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  spectroscopies are the tools for structural determination, and the signals used to identify unequivocally the amides and the enols (CH, NH, OH,  $C_\alpha$ ,  $C_\beta$ ) are described in more detail, whereas all the signals are given in Tables 4 ( $^1\text{H}$  NMR data), 5 ( $^{13}\text{C}$  NMR data) and 6 ( $^{19}\text{F}$  NMR data). For **5–6** mixtures the integrations of the minor signals (given in these tables) are in the same ratio as those of the major signals.

**The 5a/6a system.** In  $\text{CCl}_4$ . At room temperature (rt) the  $^1\text{H}$  NMR spectrum of the **5a/6a** system displays signals ascribed to a mixture of **5a** and **6a**. The six higher intensity signals are 1H signals at  $\delta$  15.59 (d,  $J = 1$  Hz), 9.02 (br) and 3.23 (hept,  $J = 6.8$  Hz), two 3H singlets at  $\delta$  2.98 and 2.84 and a 6H doublet at  $\delta$  0.48 ( $J = 6.5$  Hz) ascribed to the OH, NH, *i*-Pr-H, COOMe, COOMe and *i*-Pr-Me of enol **5a**. Signals with 0.7 H intensities at  $\delta$  6.09 (br, NH), 3.30 (s, CH), 3.20 (heptet,  $J = 6.8$  Hz, *i*-Pr-CH), 4.3H signals at  $\delta$  2.98 (s, CO<sub>2</sub>Me) and 0.40 (d,  $J = 6.6$  Hz,

**Table 3.** ACD-LAB  $^{13}\text{C}$  calculated shifts

R <sup>1</sup>	R <sup>2</sup>	A				
		C1	C4	$\Delta^a$	C3 <sup>b</sup>	C2 <sup>b</sup>
CO <sub>2</sub> Me	CO <sub>2</sub> Me	162.95	55.64	107.31	163.09	163.09
CN	CN	157.61	37.78	119.83	114.55	114.55
CN	CO <sub>2</sub> Me	160.88	42.18	118.70	160.88	118.37
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> Me	162.95	57.28	105.67	170.97	163.09
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CN	160.88	43.82	117.06	166.85	118.37
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	162.95	58.91	104.04	170.97	170.97
		EA				
		C1'	C4'	$\Delta^a$	C3' <sup>b</sup>	C2' <sup>b</sup>
CO <sub>2</sub> Me	CO <sub>2</sub> Me	167.33	77.86	89.47	160.40	161.09
CN	CN	185.42	40.44	144.98	116.01	110.26
CN	CO <sub>2</sub> Me	174.65	59.25	115.40	157.81	111.29
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> Me	167.33	74.88	92.45	165.08	160.43
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CN	174.65	56.26	118.39	162.75	117.03
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	167.33	71.89	95.44	164.49	165.15
		IA				
		C1''	C4''	$\Delta^a$	C3'' <sup>b</sup>	C2'' <sup>b</sup>
CO <sub>2</sub> Me	CO <sub>2</sub> Me	158.00	61.36	96.64	162.09	162.09
CN	CN	158.54	68.29	90.25	116.82	116.82
CN	CO <sub>2</sub> Me	158.27	62.02	96.25	160.52	119.83
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> Me	158.00	63.00	95.00	166.89	162.09
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CN	158.27	63.66	94.61	165.28	119.83
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	158.00	64.64	93.36	166.89	166.89
		EE				
		C1'''	C4'''	$\Delta^a$	C3''' <sup>b</sup>	C2''' <sup>b</sup>
CO <sub>2</sub> Me	CO <sub>2</sub> Me	158.75	55.25	103.50	159.32	163.26
CN	CN					
CN	CO <sub>2</sub> Me	156.86	66.12	90.74	166.87	119.48
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> Me	158.75	93.86	64.89	159.14	163.26
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CN	156.86	66.71	90.15	166.69	119.48
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>			90.88		
		Experimental data				
		C1	C4	$\Delta^a$	C3 <sup>b</sup>	C2 <sup>b</sup>
CO <sub>2</sub> Me	CO <sub>2</sub> Me	164.5	58.5	106	166.3	166.3
CN	CN	170.9,176.7	36.1	138.4,140.6	117.2	117.2
CN	CO <sub>2</sub> Me	171.1	55.8	115.3	171.2	116.7
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> Me	162.4,162.8	58.2	104.2,104.6	164.8	166.8
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CN	172.4	56.3	116.1	117.9	172.4
CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	169.1	71.7	97.4	166.8	172.5

<sup>a</sup>  $\Delta = \delta(1) - \delta(4)$  for A,  $\delta(1') - \delta(4')$  for EA,  $\delta(1'') - \delta(4'')$  for IA and  $\delta(1''') - \delta(4''')$  for EE.

<sup>b</sup> COOR signal at  $\delta$  157.87–179.07; CN signal at  $\delta$  110.26–119.83 ppm.

**Table 4.**  $^1\text{H}$  NMR for systems **5/6** and **7** (R and R' are the alkyl groups of Y and Y').

System	Solvent	T(K)	Chemical shift ( $\delta$ , ppm)							
			OH	NH	CH	R	R'	<i>i</i> -Pr-CH <sup>a</sup>	<i>i</i> -Pr-Me <sup>b</sup>	
<b>5a</b>	CCl <sub>4</sub>	298	15.59 <sup>c</sup>	9.02 <sup>d</sup>		2.96	2.84	3.23	0.48	
<b>6a</b>					6.09 <sup>d</sup>	3.30	2.98	2.98	3.20	0.40
<i>E</i> - <b>5b</b>			15.62	8.67		3.64 <sup>e</sup>	3.00	3.28	0.48	
<i>Z</i> - <b>5b</b>			14.60	9.15		3.71 <sup>e</sup>	2.89	—	0.49	
<b>6b</b>	CDCl <sub>3</sub>	298		6.03 <sup>d</sup>	3.43	—	2.84	—	0.40	
<b>5c</b>			14.70	8.86 <sup>f</sup>		3.74 <sup>e</sup>	3.67 <sup>e</sup>	3.32	0.51	
<b>5d</b>			14.06	6.55			3.00	3.30	0.50	
<b>5a</b>			16.32	9.74 <sup>d</sup>		3.82	3.74	4.08	1.25	
<b>6a</b>				7.11 <sup>d</sup>	4.34	3.81	—	—	1.19	
<i>E</i> - <b>5b</b>			16.29 <sup>c</sup>	9.38 <sup>d</sup>		4.50 <sup>e</sup>	3.81	4.01–4.14(m)	1.25	
<i>Z</i> - <b>5b</b>			15.35 <sup>c</sup>	9.82 <sup>d</sup>		4.55–4.65(m)	3.73	—	1.26	
<b>6b</b>				6.94	4.41	—	3.83	—	1.19	
<b>5c</b>			15.38 <sup>c</sup>	9.57 <sup>d</sup>		4.57 <sup>e</sup>	4.49 <sup>e</sup>	4.11	1.26	
<b>6c</b>				6.53	4.51	4.61 <sup>e</sup>	—	—	1.19	
<b>5d</b>			14.81(br)	6.10			3.81	4.15	1.26	
<b>6d</b>				6.58	4.50	—	3.89	—	1.21	
<b>5d</b>	240	14.72 <sup>c</sup>	6.46 <sup>f</sup>		3.83	4.14	1.28			
<b>5e</b>	298	13.95(br)	6.54 <sup>d</sup>		4.57 <sup>e</sup>	4.14	1.28			
<b>5e</b>	240	13.94	6.19 <sup>d</sup>		4.62 <sup>e</sup>	4.16	1.29			
<b>5f</b>	298	13.37(br)	6.16 <sup>d</sup>		5.79 <sup>g</sup>	4.16	1.29			
<i>Z</i> - <b>5f</b>	240	13.30	6.59		5.84 <sup>g</sup>	4.20	1.30			
<i>E</i> - <b>5f</b>			8.4		—	—	—			
<b>5h</b>	298	15.05	9.15		1.70 <sup>h</sup>	4.13	1.29			
<b>5h</b>	260	14.74	9.10		1.76 <sup>h</sup>	4.17	1.32			
<b>7</b>	298	15.10	9.39		1.71 <sup>h</sup>	—	1.47 <sup>k</sup>			
<b>7</b>	240	14.94	9.36		1.74 <sup>h</sup>	—	1.48 <sup>k</sup>			
<b>6a</b>	CD <sub>3</sub> CN	298		6.78 <sup>d</sup>	4.32	3.72	—	3.93	1.11	
<b>5a</b>			16.50	9.80		—	—	—	—	
<b>6a</b>			240	6.84 <sup>f</sup>	4.35	3.69	—	3.87	1.07	
<b>5a</b>			16.59	9.80		—	—	—	—	
<b>6b</b>			298	6.75	4.45	4.66	3.74	3.87–4.00(m)	1.12	
<b>5b</b>			16.42	9.32		—	—	—	—	
<b>6b</b>			240	6.93 <sup>f</sup>	4.48	4.67	3.71	3.89	1.07	
<b>5b</b>			16.45	9.33		—	—	—	—	
<b>5c</b>			298	15.46	9.57 <sup>d</sup>		4.60–4.80(m)	4.09	1.26	
<b>6c</b>				6.75	4.58	—	—	3.94	1.12	
<b>5c</b>			240	15.53	9.63 <sup>f</sup>		4.59 <sup>e</sup>	4.06	1.21	
<b>6c</b>				6.93 <sup>f</sup>	4.60	4.68 <sup>e</sup>	—	3.88	1.07	
<b>5d</b>	298	14.93	6.47 <sup>d</sup>			3.77	4.09	1.21		
<b>6d</b>		6.88 <sup>d</sup>	4.60	—	3.79	3.92	1.14 <sup>i</sup>			
<b>5d</b>	240	14.90	6.70 <sup>f</sup>		3.73	4.07	1.17			
<b>6d</b>		7.08 <sup>f</sup>	4.58	—	3.75	3.87	1.09 <sup>i</sup>			
<b>5e</b>	298	13.98	6.70 <sup>d</sup>		4.68 <sup>e</sup>	4.10	1.23			
<b>6e</b>		6.93 <sup>d</sup>	—	—	—	3.94	1.16 (br)			
<i>Z</i> - <b>5e</b>	240	13.94	6.91 <sup>f</sup>		4.67 <sup>e</sup>	4.10	1.18			
<i>E</i> - <b>5e</b>		—	8.79		—	—	—			
<b>6e</b>			7.14	4.58	—	3.88	—			
<b>5f</b>	298		7.04		6.17 <sup>g</sup>	4.12	1.24			
<b>6f</b>			7.58	4.60	—	—	—			
<i>Z</i> - <b>5f</b>	240	13.01	7.20 <sup>f</sup>		6.27 <sup>g</sup>	4.11	1.19			
<i>E</i> - <b>5f</b>			8.56		—	4.02	—			
<b>6f</b>			7.56	4.61	—	—	—			
<b>6g</b>	298		6.87 <sup>d</sup>	4.95	—	3.94	1.16			
<b>6g</b>	240		7.05 <sup>d</sup>	4.96	—	3.89	1.11			
<b>5h</b>	298	15.00	9.09		1.67 <sup>h</sup>	4.11	1.26			
<b>5h</b>	240	15.01	9.05		1.65 <sup>h</sup>	4.08	1.22			
<b>7</b>	298	15.26	9.36		1.67 <sup>g</sup>	—	1.44 <sup>k</sup>			
<b>7</b>	240	15.17	9.32		1.65 <sup>h</sup>	—	1.40 <sup>k</sup>			
<b>6a</b>	DMSO- <i>d</i> <sub>6</sub>	298		8.11 <sup>f</sup>	4.46	3.67	—	3.80	1.05	
<b>6b</b>				8.17 <sup>f</sup>	4.62	4.83 (m) <sup>e</sup>	3.68	3.81	1.06 <sup>i</sup>	
<b>6c</b>				8.28	4.77	4.87 <sup>e</sup>	—	3.82	1.06	
<b>6d<sup>j</sup></b>				8.56 <sup>d</sup>	4.93	—	3.69	3.87	1.12	

Table 4. continued

System	Solvent	T(K)	Chemical shift ( $\delta$ , ppm)						
			OH	NH	CH	R	R'	<i>i</i> -Pr-CH <sup>a</sup>	<i>i</i> -Pr-Me <sup>b</sup>
<b>5e</b> <sup>-j</sup>	DMF- <i>d</i> <sub>7</sub>		7.14 (br)	8.57 <sup>d</sup>			4.73 <sup>e</sup>	3.95	1.13
<b>5f</b> <sup>-j</sup>			9.5–12	7–9.5			6.37 <sup>g</sup>	3.92	1.10
<b>5g</b> <sup>-</sup>				5.55				3.89	1.09
<b>5h</b> <sup>-</sup>			15.03 (br)	9.10			1.65 <sup>h</sup>	4.06	1.24
<b>7</b> <sup>-</sup>			15.18	9.31			1.65 <sup>h</sup>		1.42 <sup>k</sup>
<b>5d</b>			14.95	8.55 <sup>d</sup>				3.78	4.12 <sup>d</sup>
<b>6d</b>				—	5.08			—	3.93
<i>Z</i> - <b>5d</b>		220	15.01	9.07 <sup>f</sup>				3.80	4.14
<i>E</i> - <b>5d</b>				9.18 <sup>f</sup>				3.61	4.06
<b>6d</b>				9.16 <sup>f</sup>	5.21			3.80	3.89
<b>5e</b> <sup>-</sup>				8.87 <sup>d</sup>				4.86 <sup>c</sup>	4.12 <sup>d</sup>
<b>5e</b>		220	14.10	9.36 <sup>f</sup>				5.09 <sup>e</sup>	4.16 <sup>d</sup>
<b>5e</b> <sup>-</sup>				8.95				4.92 <sup>c</sup>	4.07
<b>5f</b> <sup>-</sup>		220	8.7–12	8.32 <sup>d</sup>				6.89 <sup>g</sup>	4.03
<b>6f</b>					5.57				
<b>5f</b> <sup>-</sup>	298		8.49 <sup>d</sup>				6.51 <sup>g</sup>	4.10	
<b>6f</b>				5.22					
<b>5g</b>	220	12–17	8.56 <sup>f</sup>					4.07	
<b>5g</b> <sup>-</sup>	298							4.05	
<b>5h</b>	220	15.21	9.27			1.72 <sup>h</sup>		4.15	
<b>5h</b> <sup>-</sup>	298	15.68	9.20			1.69 <sup>h</sup>		4.14	
<b>7</b> <sup>-</sup>	298	15.42	9.4			1.70 <sup>h</sup>			
<b>7</b>	220	15.33	9.40			1.72 <sup>h</sup>			
<i>Z</i> - <b>5f</b>	THF- <i>d</i> <sub>8</sub>	180	13.20	8.77 <sup>f</sup>			6.91 <sup>g</sup>	4.19	1.22
<i>E</i> - <b>5f</b>			11.62	8.83 <sup>f</sup>			6.73 <sup>g</sup>	4.07	—
<i>Z</i> - <b>5f</b>		240	13.39	8.53 <sup>d</sup>			6.66 <sup>d</sup>	4.17 <sup>d</sup>	1.24
<i>E</i> - <b>5f</b>			11.16	8.76 <sup>d</sup>			6.46 <sup>d</sup>	—	—
<b>5f</b>		298	10–16	8.31 <sup>d</sup>			6.32	4.14	1.25
<b>5g</b>		180	12.93	8.10 <sup>f</sup>				4.01	1.16
<b>6g</b>				8.34 <sup>f</sup>	5.38			3.89	—
<b>5g</b>		240	12.32	7.74 <sup>f</sup>				4.00	1.18
<b>6g</b>				8.04 <sup>d</sup>	5.29			3.96	1.15
<b>5g</b>		298	10–13	7.35 <sup>d</sup>				4.00	1.18
<b>6g</b>				7.68 <sup>d</sup>	5.18			—	—
<b>5h</b>		180	15.42	9.23			1.66 <sup>h</sup>	4.14	1.26
<b>5h</b> '			11.63	9.28					
<b>5h</b>		240	15.46	9.22			1.65 <sup>h</sup>	4.12	1.26
<b>5h</b> '			11.22						
<b>5h</b>	298	15.37	9.22			1.64 <sup>h</sup>	4.12	1.27	
<b>5h</b> '		10.82							

<sup>a</sup> Octet,  $J = 6.7$ – $7.2$  Hz.

<sup>b</sup> d,  $J = 6.5$ – $6.6$  Hz.

<sup>c</sup> d,  $J = 1$ – $1.5$  Hz.

<sup>d</sup> br.

<sup>e</sup> q,  $J = 8.4$ – $9.4$  Hz.

<sup>f</sup> d,  $J = 5.2$ – $7.8$  Hz.

<sup>g</sup> Heptet,  $J = 5.9$ – $6.2$  Hz.

<sup>h</sup> For **5h/6h** and **7**, R = CMe<sub>2</sub>.

<sup>i</sup> 2d,  $J = 6.2$  Hz.

<sup>j</sup> All peaks are not sharp.

<sup>k</sup> The t-Bu singlet.

*i*-Pr-Me) were assigned to the amide **6a**. The **5a/6a** ratio is 59:41. The low-field  $\delta$ (OH),  $\delta$ (NH) of **5a** indicate strong hydrogen bonding, whereas the two COOMe signals indicate that rotation around the C=C bond at room temperature is slow on the NMR time-scale. Enol–amide tautomerization is apparently slow under these conditions.

The <sup>13</sup>C NMR spectrum displays signals for both

species. The three lowest field signals are for **5a** at  $\delta$  174.68 and 169.30 (2 COO q at different environment in the H-coupled spectrum) and 171.92 (=C<sub>α</sub>). C<sub>β</sub> for **5a** is at  $\delta$  74.83 (s) [ $\Delta C_{\alpha\beta} \approx 97$  ppm] and the two MeO q are at  $\delta$  51.61, 50.65 ( $J = 146$  Hz). The signals of **6** are at  $\delta$  165.76 (COO, twice the C<sub>α</sub> signal intensity), 159.54 (C<sub>α</sub>), 58.33 (CH, d,  $J = 136$  Hz), 52.76 (q,  $J = 147$  Hz, OMe).



Table 5. <sup>13</sup>C NMR data for systems 5/6 and 7

System	Solvent	T(K)	COO	CON or C <sub>α</sub>	CF <sub>3</sub> <sup>a</sup>	CN	Chemical shift (δ, ppm)			i-Pr-CH <sup>e</sup>	i-Pr-Me <sup>f</sup>
							CH <sub>2</sub> CF <sub>3</sub> <sup>b</sup> or CH(CF <sub>3</sub> ) <sub>2</sub> <sup>c</sup>	CH or C <sub>β</sub>	OMe <sup>d</sup>		
5a	CCl <sub>4</sub>	298	174.68, 169.20	171.92			74.83	51.61, 50.65	42.35	23.00	
6a			165.76	159.54			58.33 <sup>g</sup>	52.76	41.67	22.64	
E-5b			174.48, 167.16	171.79	123.39		74.31	59.70	42.61	22.89	
Z-5b			172.28, 168.98	171.79	123.14		74.66	60.42	42.70	—	
6b			165.64, 163.54	158.87	—		57.84 <sup>g</sup>	—	41.90	22.51	
6c			172.21, 167.00	171.42	123.16, 122.90		74.21	60.87, 60.16	43.04	22.74	
6d			173.67	171.27		115.76	55.83	51.70	43.74	22.40	
5a		CDCl <sub>3</sub>	298	174.81, 169.77	171.58		74.77	52.05, 51.02	42.58	22.60	
6a				166.12	160.83			58.58 <sup>g</sup>	53.26	41.96	22.23
E-5b				174.71, 167.40	171.51	123.38		74.35	59.74	42.86	22.62
Z-5b			172.40, 169.60	170.19	—		74.70	60.47	42.95	22.55	
6b			165.70, 164.04	160.01	123.39		58.24 <sup>g</sup>	61.42	42.26	22.27	
5c			172.23, 167.21	171.14	123.18, 122.94		74.17	60.80, 60.10	43.20	22.44	
6c			163.51	159.14	122.26		58.05 <sup>g</sup>	61.62	41.91	22.34	
5d			173.58 <sup>h</sup>	171.32		116.77	55.98	52.12	43.79	22.46	
5d	240		173.41 <sup>h</sup>	170.57		117.17	55.44	52.32	43.66	22.35	
5e	298		171.06	170.97	122.67		56.04	60.22	44.28	22.25	
5e	240	170.68	170.50	122.40		55.88	59.89	44.10	22.45		
5f	298	169.37	170.97	120.76		56.57	66.84	45.07	22.57		
5f	240	168.61	170.13	120.00		55.95	65.81	44.51	22.25		
5h	298	169.43, 164.26	170.43	104.54		72.72	26.23	43.36	22.51		
5h	260	168.35, 164.25	170.03	104.60		72.43	25.97	43.13	22.34		
6a	CD <sub>3</sub> CN	298	165.84 <sup>i</sup>	161.57			58.91 <sup>g</sup>	52.58	41.83	21.35	
6b			165.18, 163.96 <sup>j</sup>	160.86	123.11		58.56 <sup>g</sup>	60.96	41.98	21.27	
6b		240	164.96 <sup>h</sup> , 163.71 <sup>j</sup>	160.75	122.77		57.94 <sup>g</sup>	60.49	41.54	20.89	
5c		298	171.23, 166.84	171.23	123.60		73.70	60.36	43.29	21.52	
6c			163.34 <sup>m</sup>	160.17	123.06		58.26 <sup>g</sup>	61.67	42.16	21.21	
5c		240	171.85, 166.58	170.58	—		73.16	60.22	42.80	21.80	
6c			163.12	160.76	122.71		57.64	60.66	41.66	20.83	
5d		298	174.04	171.22		116.01	55.56	51.90	43.79	21.35	
6d			163.09	158.54		113.55 <sup>k</sup>	45.78 <sup>g</sup>	53.68	42.67	21.13	
5d		240	173.63 <sup>h</sup>	170.36		115.92	54.86	51.73	43.22	20.92	
6d		162.82	158.19		113.48 <sup>k</sup>	45.50 <sup>g</sup>	53.52	42.18	20.73		
5e	298	171.40	170.86	123.34		55.70	60.11	44.23	21.21		
5f	240	170.91	169.98	122.99		55.03	59.58	43.61	20.79		
5f	298	168.47	170.12	120.75		55.91	66.06	44.55	21.13		
5f	240	168.29	169.40	120.28		55.22	65.16	43.94	20.64		
6g	298 <sup>l</sup>		155.23		110.65	31.12 <sup>g</sup>	—	43.54	20.97		
6g	240		154.82		110.30 <sup>k</sup>	30.80 <sup>g</sup>	—	42.88	20.58		
5h	298		169.51	104.41		72.70	25.23	43.22	21.46		
5h	240	170.15, 163.57	168.76	104.10		72.32	24.69	42.76	21.00		
7	298	170.53, 164.38	170.15	104.34		73.04	26.00	53.66	28.96		
6a	DMSO-d <sub>6</sub>	240	170.27, 164.38	169.54		72.84	26.01	104.37	53.57	26.01	
6b		298	165.54 <sup>i</sup>	161.35	123.13		58.59 <sup>g</sup>	52.57	41.10	21.97	
			164.96, 163.72	160.70		58.21 <sup>g</sup>	60.53	52.74	41.20	21.89	

Table 5. continued

System	Solvent	T(K)	Chemical shift ( $\delta$ , ppm)									
			COO	CON or C $\alpha$	CF $_3$ <sup>a</sup>	CN	CH <sub>2</sub> CF $_3$ <sup>b</sup> or CH(CF $_3$ ) $_2$ <sup>c</sup>	CH or C $\beta$	OMe <sup>d</sup>	<i>i</i> -Pr-CH <sup>e</sup>	<i>i</i> -Pr-Me <sup>f</sup>	
<b>6c</b>			163.20 <sup>m</sup>	160.09	123.09		60.76	57.85 <sup>g</sup>	41.32	21.80		
<b>5d</b> <sup>l</sup>			171.35	163.23		117.51		55.81	42.35	22.05		
<b>6d</b>			169.22	158.64		114.45		53.44	45.50	—		
<b>5e</b> <sup>-l</sup>			167.97		123.58	117.84	58.64	56.39	42.17	22.27		
<b>5f</b> <sup>l</sup>			164.95		121.12	119.15	64.64	57.12	41.32	22.63		
<b>5g</b> <sup>-</sup>				167.34		118.20		33.56	43.07	22.24		
<b>5h</b> <sup>-</sup>			166.44	168.11 <sup>n</sup>			25.27	72.29	42.98	21.73		
<b>7</b> <sup>-</sup>			166.72	169.42	104.27		25.55	72.65	53.23	28.33		
<b>5d</b> <sup>l</sup>	DMF- <i>d</i> <sub>7</sub>	298	174.82	170.99	104.27	116.53		56.07	44.04	22.15		
<b>6d</b>			164.05	159.69		114.76 <sup>k</sup>		46.19 <sup>g</sup>	42.86	—		
<b>Z-5d</b>		220	175.13	170.84		117.24		55.81	44.18	22.38		
<b>E-5d</b>			170.73	169.41		120.06		57.70	43.87	22.38		
<b>6d</b>			164.69	160.19		115.66 <sup>k</sup>		46.74 <sup>g</sup>	43.05	23.02		
<b>5e</b> <sup>-</sup>		298 <sup>l</sup>	170.13		124.47	117.05	60.09	56.95	44.06	22.35		
<b>5e</b> <sup>-</sup>		220	172.30	170.39		124.82	60.80	55.85	44.54	22.26		
<b>5e</b> <sup>-</sup>			169.56	168.35		125.15	59.48	57.65	43.92	22.89		
<b>5f</b> <sup>-</sup>		220	166.29	169.08		122.53	65.06	58.07	43.05	23.03		
<b>5f</b> <sup>-</sup>		298	166.62	169.33		122.10	65.98	57.71	43.36	22.71		
<b>5g</b> <sup>-</sup>		298 <sup>l</sup>		169.06		117.38		34.51	44.25	22.32		
<b>5g</b> <sup>-</sup>		220		170.64		119.48, 118.99		34.85	44.34	22.63		
<b>5h</b> <sup>-</sup>		220	171.59	169.68			26.00	73.54	44.24	22.22		
<b>5h</b> <sup>-</sup>		298	167.76	169.98	105.51		25.99	73.30	44.02	22.20		
<b>7</b> <sup>-</sup>		298	167.86	170.90	105.13		25.96	73.67	54.14	28.82		
<b>7</b>	THF- <i>d</i> <sub>8</sub>	220	171.68, 164.94	170.86	105.61		25.98	73.96	54.38	28.72		
<b>5f</b>		298	169.08	170.80	121.97	114.54 <sup>n</sup>		57.18	45.04	22.25		
<b>Z-5f</b>		240	170.01	170.80	121.99	114.15 <sup>n</sup>		56.63	44.98	22.09		
<b>E-5f</b>			—	—	—	—		—	—	—		
<b>Z-5f</b>		180	169.41	170.27	122.22	114.54 <sup>n</sup>		56.23	44.78	22.02		
<b>E-5f</b>			165.70	169.02	121.96	116.79 <sup>n</sup>		57.05	44.46	22.30		
<b>5g</b>		298 <sup>l</sup>		170.67		116.19		36.63	45.07	22.40		
<b>6g</b>				156.00		111.37		31.30 <sup>g</sup>	—	—		
<b>5g</b>		240		170.43		116.77, 116.61		36.15	45.05	22.54		
<b>6g</b>				156.19		115.59 <sup>k</sup>		31.44 <sup>g</sup>	43.70	22.19		
<b>5g</b>		180		170.11		117.39, 117.06		35.52	44.80	22.52		
<b>6g</b>				156.45		112.10 <sup>k</sup>		32.01 <sup>g</sup>	—	—		
<b>5h</b>		298	171.44, 164.26	170.71	104.88		26.16	44.06	44.06	22.48		
<b>5h</b>		240	171.54, 164.17	170.32	105.00		25.97	44.05	44.05	22.37		
<b>5h</b>		180	171.54, 164.00	169.80	105.20		25.71	44.05	44.05	22.09		

<sup>a</sup> q,  $J = 277$ – $285$  Hz, for **5h/6h** and **7**, the signal of CMMe $_2$ ; <sup>b</sup> tq,  $J_t = 150$  Hz,  $J_q = 35$ – $37$  Hz, for **5h/6h** and **7**, the signal of CMMe $_2$ .

<sup>c</sup> dm,  $J_d = 152$ – $153$  Hz,  $J_m = 34$ – $35$  Hz; <sup>d</sup> q,  $J = 147$ – $149$  Hz, for **7**, the signal of CMMe $_2$ .

<sup>e</sup> dm,  $J_d = 133$ – $146$  Hz,  $J_m = 2.8$ – $4.0$  Hz, for **7**, the signal of *t*-Bu-Me; <sup>f</sup> qm,  $J_q = 125$ – $127$  Hz,  $J_m = 4.0$  Hz; <sup>g</sup> d,  $J = 132$ – $136$  Hz; <sup>h</sup> q,  $J = 3.9$  Hz.

<sup>i</sup> dq,  $J_d = 7.9$  Hz,  $J_q = 4.0$  Hz; <sup>j</sup> d,  $J = 8.6$  Hz; <sup>k</sup> d,  $J = 10.4$ – $12.9$  Hz; <sup>l</sup> All peaks are not sharp. <sup>m</sup> dt,  $J_d = 8.7$  Hz,  $J_t = 3.0$  Hz; <sup>n</sup> Overlap with THF at 66–68 ppm.

**Table 6.**  $^{19}\text{F}$  NMR data ( $\delta$  in ppm) for systems **5/6**

System	Solvent	<i>T</i> (K)	$\text{CH}_2\text{CF}_3^{\text{a}}$ or $\text{CH}(\text{CF}_3)_2^{\text{b}}$			
			<i>E</i> -Enol	<i>Z</i> -Enol	Amide	Ion
<b>5b/6b</b>	$\text{CCl}_4$	298	-75.29	-75.35	-75.25	
<b>5c/6c</b>			-75.62			
<b>5b/6b</b>	$\text{CDCl}_3$	298	-74.66	-74.70	-74.52	
<b>5c/6c</b>			-74.80 <sup>e</sup>		-74.57	
<b>5e/6e</b>			-74.76			
		240	-74.43			
<b>5f/6f</b>		298	-74.09			
		240	-74.06	-73.92		
<b>5b/6b</b>	$\text{CD}_3\text{CN}$	240			-75.26	
						-75.18
<b>5c/6c</b>		298	-75.27		-75.17	
		240	-75.24		-75.22	
<b>5e/6e</b>		298	-75.52		-75.27	
		240	-75.40		-75.20	
<b>5f/6f</b>		298	-75.03 <sup>d</sup>			
		240	-75.06 <sup>d</sup>			
<b>5b/6b</b>	$\text{DMSO-}d_6$	298			-73.20	-73.36
<b>5e/6e</b>						
<b>5f/6f</b>					-73.17	
<b>5e/6e</b>	$\text{DMF-}d_7$	220			-74.74 <sup>c</sup>	-74.92
<b>5f/6f</b>						-74.55 <sup>c</sup>
		298				
		220				-74.47
	$\text{THF-}d_8$	298	-77.03			
			180	-77.02 <sup>d</sup>		

<sup>a</sup> *t*,  $J = 7.5\text{--}9.0$  Hz.

<sup>b</sup> *d*,  $J = 4.9\text{--}7.1$  Hz.

<sup>c</sup> *m*.

<sup>d</sup> The signals for *E*-enol, *Z*-enol and amide overlap.

<sup>e</sup> The signals for amide and ion overlap.

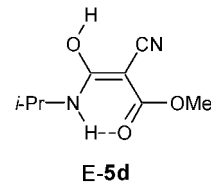
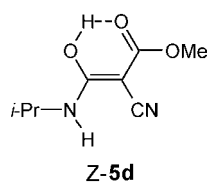
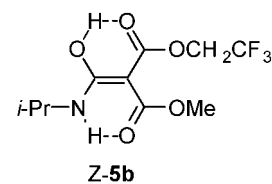
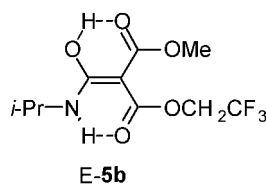
*in CDCl<sub>3</sub>*. The  $^1\text{H}$  NMR signals for both **5a** and **6a** resemble those in  $\text{CCl}_4$  (Table 4) but the **5a/6a** ratio of 9:91 is much lower than in  $\text{CCl}_4$ . Both the OH and NH of **5a** at  $\delta$  16.32 and 9.74 are at a significantly lower field than in  $\text{CCl}_4$ . The  $^{13}\text{C}$  NMR spectrum resembles that in  $\text{CCl}_4$  except for slightly shifted  $\delta$  values (Table 5).

*in CD<sub>3</sub>CN*. The *rt*  $^1\text{H}$  NMR signals display  $\delta$ s and integration for the amide **6a** (Table 4) with <1% OH and NH enol signals at  $\delta$  16.50 (16.59 at 240 K) and 9.80, respectively. At 240 K, the spectrum is very similar except that the NH signal of **6a** is a sharper doublet. The  $^{13}\text{C}$  NMR spectrum displays signals for the amide (Table 5).

*in DMSO-*d*<sub>6</sub>*. Both the  $^1\text{H}$  and the  $^{13}\text{C}$  NMR spectra resemble those in  $\text{CD}_3\text{CN}$ , with  $\delta$  values differing by <0.2 ppm, except for  $\delta(\text{NH})$  at 8.11, compared with  $\delta$ 6.78 in  $\text{CD}_3\text{CN}$ , probably due to hydrogen bonding in  $\text{DMSO-}d_6$ .

**The 5b/6b system.** *in CCl<sub>4</sub>*. Owing to inequivalent ester groups, two enols can be formed.<sup>3c</sup> Indeed, the  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra show the presence of two enols and

the amide. Unfortunately, crystals suitable for x-ray diffraction were not obtained. The *E* and *Z* assignments of the enols are based on the  $\delta(\text{OH})$  and  $\delta(\text{NH})$  as shown previously and discussed below. In the  $^1\text{H}$  NMR spectrum the major enol (*E*-**5b**) signals are at  $\delta$  15.62 (s, OH), 8.67 (s, NH), 3.64 (q,  $J = 8.5$  Hz,  $\text{CH}_2\text{CF}_3$ ), 3.28 (m, *i*-Pr-CH), 3.00 (s, MeO) and 0.48 (d,  $J = 6.5$  Hz, *i*-Pr-Me); the corresponding signals for *Z*-**5b** are at  $\delta$  14.60, 9.15, 3.71, 2.89 and 0.49. Those for **6b** are at  $\delta$  6.03 (br, NH), 3.43 (s, CH), 2.84 (s, MeO) and 0.40 (d,  $J = 6.6$  Hz,



*i*-Pr-Me). The **E-5b**:**Z-5b**:**6b** ratio is 65: 26: 9. The  $^{19}\text{F}$  NMR spectrum displays three signals at  $\delta -75.29$  (t,  $J=9.0$  Hz, **E-5b**),  $-73.35$  (t,  $J=8.7$  Hz, **Z-5b**) and  $-75.25$  (**6b**) in a 63:29:8 ratio, which are identified by the similar ratio in the  $^1\text{H}$  NMR spectrum.

The  $^{13}\text{C}$  NMR spectrum shows the signals for **E-5b**, **Z-5b** at  $\delta$  174.48, 172.28 (COO), 171.79, 171.79 ( $\text{C}_\alpha$ ), 167.16, 168.98 (COO) and 74.31, 74.66 ( $\text{C}_\beta$ ) and for **6b** at  $\delta$  165.64, 163.54 (COO), 158.87 ( $\text{C}_\alpha$ ), 57.84 ( $\text{C}_\beta$ ). Other signals are given in Table 6.

*In CDCl<sub>3</sub>*. The rt  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra resemble those in  $\text{CCl}_4$  except that the signals appear at a lower field, as shown in Tables 4 and 6. The **E-5b**:**Z-5b**:**6b** ratio is 34:16:50. The  $^{13}\text{C}$  NMR spectrum resembles that in  $\text{CCl}_4$ , with minor differences.

*In CD<sub>3</sub>CN and DMSO*. In  $\text{CD}_3\text{CN}$  the  $^1\text{H}$  NMR spectrum indicates the presence of >99% of the amide **6b**. Some  $\text{CH}_2$  signals are doubled owing to their diastereotopicity. Signals of <1% at  $\delta$  16.42 and 9.32 at rt and 240 K are ascribed to traces of **5b**.

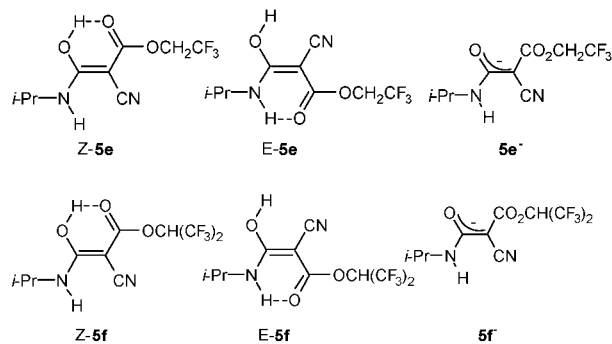
The  $^{13}\text{C}$  NMR spectrum in  $\text{CD}_3\text{CN}$  at rt displays amide signals at  $\delta$  165.18 ( $\text{CO}_2\text{Me}$ ), 163.96 ( $\text{CO}_2\text{CH}_2\text{CF}_3$ ), 160.86 ( $\text{C}_\alpha$ ) and 58.56 ( $\text{C}_\beta$ ). Other signals are given in Table 5.

In  $\text{DMSO}-d_6$  the  $^1\text{H}$  NMR spectrum resembles that in  $\text{CD}_3\text{CN}$  except that  $\delta(\text{NH})$  is at 1.42 ppm lower field. The  $^{13}\text{C}$  NMR spectrum (Table 5) also fits the amide structure.

**The 5c/6c system.** *In CCl<sub>4</sub> and CDCl<sub>3</sub>*. In the rt  $^1\text{H}$  NMR spectrum in  $\text{CCl}_4$  only enol signals are observed [ $\delta$  14.70 (OH), 8.86 (d, NH)]. The  $^{19}\text{F}$  NMR spectrum displays one signal at  $\delta -75.62$ . The  $^{13}\text{C}$  NMR spectrum (Table 5) shows COO,  $\text{CH}_2$  and  $\text{CF}_3$  signals for two  $\text{COOCH}_2\text{CF}_3$  groups, indicating a slow rotation around the  $\text{C}_\alpha=\text{C}_\beta$  bond on the NMR time-scale at rt. In  $\text{CDCl}_3$  the **5c/6c** ratio at rt is 90:10.

*In CD<sub>3</sub>CN and DMSO-*d*<sub>6</sub>*. In  $\text{CD}_3\text{CN}$  the signals for **5c** are smaller (21% by  $^1\text{H}$ , 24% by  $^{19}\text{F}$  NMR) than for **6c** (Table 4). The rt  $^{19}\text{F}$  NMR spectrum shows two triplets at  $-75.17$  (**6c**) and  $-75.27$  (**5c**) ppm. The rt  $^{13}\text{C}$  NMR spectrum shows signals for **5c**, **6c** at  $\delta$  171.23, 160.17 ( $\text{C}_\alpha$ ), 73.70, 58.26 ( $=\text{C}_\beta$ ). In  $\text{DMSO}-d_6$  the spectra (Tables 4–6) show signals at rt only for **6c**.

**The 5d/6d system.** *In CCl<sub>4</sub> and CDCl<sub>3</sub>*. Only signals for **5d** are observed in  $\text{CCl}_4$ .  $^1\text{H}$  NMR:  $\delta$  14.06 (s, OH), 6.55 (s, NH). In  $\text{CDCl}_3$  at rt, 98% of **5d** [ $\delta$  14.81 (br, OH), 6.10 (s, NH)] is accompanied by 2% of **6d** [ $\delta$  6.58 (s, NH), 4.50 (s, CH)]. At 240 K no **6d** is observed. The  $^{13}\text{C}$  NMR spectra in  $\text{CCl}_4$  (298 K) and  $\text{CDCl}_3$  (240 K) show only signals for **5d**, e.g.  $\delta$  171.27 ( $\text{C}_\alpha$ ), 55.83 ( $=\text{C}_\beta$ ). Other signals are given in Tables 4–6.



Form E.

*In CD<sub>3</sub>CN, DMF-*d*<sub>7</sub> and DMSO-*d*<sub>6</sub>*. In  $\text{CD}_3\text{CN}$  the rt and 240 K  $^1\text{H}$  NMR spectra display signals for both **5d** and **6d**:  $\delta$  (rt) 14.93 (br, OH, **5d**), 6.47, 6.88 (br, NH, **5d**, **6d**). From the NH signals the **5d/6d** ratios are 63:37 (298 K) and 81:19 (240 K). The  $^{13}\text{C}$  NMR spectra in  $\text{CD}_3\text{CN}$  display signals for **5d** and **6d** at both 298 and 240 K (Table 5).

In  $\text{DMF}-d_7$  at rt, signals for both **5d** and **6d** are observed.  $^1\text{H}$  NMR:  $\delta$  14.95 (br, OH, **5d**), 8.55 (br, NH, **5d**, **6d**), 5.08 (br, CH, **6d**). At 220 K the signals sharpen and two enols and **6d** are observed.  $\delta$  (**Z-5d**) 15.01 (s, OH), 9.07 (d, NH), 3.80 (MeO);  $\delta$  (**E-5d**) 9.18 (d, NH), 3.61 (MeO);  $\delta$  (**6d**) 9.16 (d, NH), 5.21 (CH), 3.80 (MeO). The **Z-5d**:**E-5d**:**6d** ratio is 58:24:18. On shaking with  $\text{D}_2\text{O}$  at 298 and 220 K, the OH, NH and CH signals disappear.

The  $^{13}\text{C}$  NMR spectrum at 220 K also displays the three species (Table 5) but at rt mostly broadened signals for **6d** and only one enol were observed.

In  $\text{DMSO}-d_6$  at rt the signals are broad.  $^1\text{H}$  NMR:  $\delta$  8.56 (NH), 4.93 (CH).  $^{13}\text{C}$  NMR:  $\delta$  171.35, 163.23, 169.22, 158.64 (COO,  $\text{C}_\alpha$ ), 117.51, 114.45 (CN), 55.81 ( $=\text{C}_\beta$ ), 53.44 (CH). The spectra are consistent with the presence of both **6d** and one enol.

**The 5e/6e system.** *In CDCl<sub>3</sub>*. At rt the broad  $^1\text{H}$  NMR signals (Table 4) which sharpen at 240 K and the  $^{13}\text{C}$  NMR signals (Table 5) show the presence of only **5e**.

*In CD<sub>3</sub>CN*. Except for broad enols signals at  $\delta$  13.98, 6.70 (OH, NH), weaker signals for **6e** are observed at  $\delta$  6.93 (br, NH), 3.94 (CH). The  $^{19}\text{F}$  NMR signals are for **5e** ( $\delta -75.52$ ) and **6e** ( $\delta -75.27$ , br). By integration of the  $\text{N}^1\text{H}$  and the  $^{19}\text{F}$  signals the **5e/6e** ratio is 83:17. At 240 K all the signals sharpen and a new  $^1\text{H}$  singlet at  $\delta$  8.79 (NH) indicate the presence of a 3% of the *E*-enol. The **Z-5e**:**E-5e**:**6e** ratio is 91:3:6. In the  $^{13}\text{C}$  NMR spectra (rt, 240 K) only signals for **Z-5e** are observed (Table 5).

*In DMSO-*d*<sub>6</sub>*. The rt spectra indicate an ionization–dissociation process. The  $^1\text{H}$  NMR spectrum displays two broad signals at  $\delta$  8.57 (NH), 7.14 (CH or OH) which disappear on shaking with  $\text{D}_2\text{O}$ . Only one  $^{19}\text{F}$  NMR

signal is observed at  $\delta - 73.36$ . The rt  $^{13}\text{C}$  NMR spectrum displays a broad C=O signal at  $\delta 167.97$ , a  $\text{CF}_3$  quartet, a broad CN and  $\text{CH}_2$  and *i*-Pr signals (Table 5).

*In DMF- $d_7$* . The rt  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  spectra resemble those in  $\text{DMSO-}d_6$ , but at 220 K the spectrum is different: signals for 29% enol [ $\delta 14.10$  (OH), 9.36 (d, NH), 5.09, 4.16, 1.25 ( $\text{CH}_2\text{CF}_3$ , *i*-Pr)] are superimposed on the main signals at  $\delta 8.95$  (d, NH), 4.92, 4.07, 1.21 ( $\text{CH}_2$  and *i*-Pr) ascribed to the ion. The  $^{13}\text{C}$  NMR signals at 220 K are sharp and consistent with a mixture of enol **5e** [ $\delta 172.30$  (COO), 170.39 ( $\text{C}_\alpha$ ), 55.85 ( $=\text{C}_\beta$ )] and an ion.

**The 5f/6f system.** *In  $\text{CDCl}_3$* . The  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  spectra at rt and 240 K fit the structure *E-5f*. The  $^1\text{H}$  NMR spectrum at rt shows broad OH and NH and other signals (Table 4) which sharpen at 240 K, where an additional new 0.06 H signal appears at  $\delta 8.4$  and assigned to the NH of the enol isomer *Z-5f*. The rt  $^{19}\text{F}$  NMR spectrum displays a doublet at  $\delta - 74.09$  but two doublets at  $\delta - 73.92$  and  $- 74.06$  at 240 K, indicating the presence of two species. The 240 K rt  $^{13}\text{C}$  NMR spectra display signals for *E-5f* (Table 5).

*In  $\text{CD}_3\text{CN}$* . The NH signals at  $\delta 7.04$  and 7.58 at rt give a **5f:6f** ratio of 92:8. An OH enol signal is not observed, whereas the amide CH signal appears at  $\delta 4.6$ . However, at 240 K a broad OH signal ( $\delta 13.01$ ) and two new signals at  $\delta 8.56$  (br, NH) and 4.02 (br, *i*-Pr-CH), assigned to *E-5f*, were observed. The *Z-5f:E-5f:6f* ratio is 79:15:6. Only one  $^{19}\text{F}$  NMR doublet at  $\delta - 75.06$  is observed at both rt and 240 K.

The rt  $^{13}\text{C}$  NMR  $\text{C}_\alpha$ , COO, CN and  $=\text{C}_\beta$  signals are singlets at  $\delta 170.12$ , 168.47, 114.47 and 55.91. The spectrum at 240 K is similar. These data suggest that the ion **5f $^-$**  derived from **5f/6f** is not formed. Hence **5f $^-$**  was prepared both at 240 and 298 K by adding one drop of  $\text{Et}_3\text{N}$  into the  $\text{CD}_3\text{CN}$  solution of the sample. The  $^1\text{H}$  NMR spectrum shows that the amide CH signal has disappeared and two very broad signals appear at  $\delta 8.74$  (0.18H, presumably the ionized proton) and 7.48 (0.72H, NH). There are also two heptets at  $\delta 6.14$  [ $\text{CH}(\text{CF}_3)_2$ ] and 4.10 (*i*-Pr-CH), a *i*-Pr-Me doublet and  $\text{Et}_3\text{NH}^+$  signals at  $\delta 3.15$  ( $\text{CH}_2$ ) and 1.24 (Me). The  $^{13}\text{C}$  NMR signals are shifted: the  $\Delta\delta$  [=  $\delta$  (with  $\text{Et}_3\text{N}$ ) -  $\delta$  (without  $\text{Et}_3\text{N}$ )] values at 240 K are  $- 0.36$ ,  $- 1.2$ , 0.23,  $- 0.39$ , 0.6,  $- 1.1$  and 0.38 for the COO,  $\text{C}_\alpha$ ,  $\text{CF}_3$ ,  $\text{CH}(\text{CF}_3)_2$ , CN, *i*-Pr-CH and *i*-Pr-Me signals, respectively.

*In THF- $d_8$* . Whereas at rt very broad OH and NH signals appear at  $\delta 10-16$  and 8.31, at 240 K there are two broad enol NH signals, which give a *Z-5f:E-5f* ratio of 69:31. At 180 K all the signals of the two enols are observed and the *Z-5f:E-5f* ratio is 50:50. For *Z-5f(E-5f)*  $\delta 13.20$  (11.62) and 8.77 (8.83). Other signals are given in Table 4. Only one  $^{19}\text{F}$  NMR doublet at  $\delta - 76.84$  appears at 180 K but

$^{13}\text{C}$  NMR signals were observed for both enols.  $\delta$  (*E-5f*, *Z-5f*) 170.27, 169.02 ( $\text{C}_\alpha$ ), 57.05, 56.23 ( $=\text{C}_\beta$ ). Other signals are given in Table 5

*In  $\text{DMSO-}d_6$  and  $\text{DMF-}d_7$* . In these solvents the compound is probably ionized at rt to **5f $^-$** . In the  $^1\text{H}$  NMR spectrum in  $\text{DMSO-}d_6$  there are very broad, barely seen, acidic proton at  $\delta 9.5-12$  and NH signal at  $\delta 7.0-9.5$ . The  $^{19}\text{F}$  NMR spectrum shows a doublet at  $\delta - 73.44$  at rt. The  $^{13}\text{C}$  NMR signals are given in Table 5.

The  $^1\text{H}$ ,  $^{19}\text{F}$  and  $^{13}\text{C}$  spectra in DMF at 298 and 220 K resemble those in  $\text{DMSO-}d_6$  except that at 220 K a broad signal appears at  $\delta 8.7-12$  and the other signals are sharp, including a very small CH amide signal at  $\delta 5.57$ . On adding a drop of an aqueous 3 N NaOH solution all the  $^1\text{H}$ ,  $^{19}\text{F}$  and  $^{13}\text{C}$  NMR signals at rt or 220 K became sharper. The  $\text{C}_\beta$  signal shifts downfield by 1.18 (220 K) and 1.43 (298) ppm and  $\text{C}_\alpha$  shifts upfield by 0.99 and 1.29 ppm at 298 and 220 K, respectively.

**The 5g/6g system.** The solubility of the dicyano-substituted system in  $\text{CCl}_4$  and  $\text{CDCl}_3$  is too low to permit determination of the NMR spectrum.

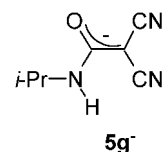
*In THF- $d_8$  and  $\text{CD}_3\text{CN}$* . In  $\text{THF-}d_8$  at rt there are  $^1\text{H}$  NMR OH signals at  $\delta 10-13$ , (vb), NH at 7.35 (br) and *i*-Pr ( $\delta 4.00$ , 1.18) for **5g** and broad amide signals at  $\delta 7.68$  (NH) and 5.18 (CH). From the NH signals the rt **5g:6g** ratio is 60:40. At 180 K all the signals sharpen except for the  $\delta\text{OH}$  at 12.93. The **5g:6g** ratios are 96:4 (180 K) and 81:19 (240 K). The OH, NH and CH signals disappear on shaking with  $\text{D}_2\text{O}$  at rt or 240 K.

The  $^{13}\text{C}$  NMR signals (Table 5) which are not sharp at rt sharpen at 180 K. The two CN signals for **5g** indicate a hindered rotation around the  $\text{C}_\alpha=\text{C}_\beta$  bond at 180 K.

In  $\text{CD}_3\text{CN}$  the spectra at both rt and 240 K indicate the presence of only **6g** (Tables 4 and 5). The signals are broadened at rt.

*In  $\text{DMSO-}d_6$  and  $\text{DMF-}d_7$* . In  $\text{DMSO-}d_6$  only *i*-Pr protons are observed (Table 4), suggesting an ionization of the OH or CH species to **5g $^-$** . This is consistent with the  $\text{C}_\beta$  singlet at 33.56 in the hydrogen-coupled  $^{13}\text{C}$  spectrum. Other signals are given in Table 5.

In  $\text{DMF-}d_7$  the rt  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra resemble those in  $\text{DMSO-}d_6$ , but the  $^1\text{H}$  NMR spectrum at 220 K display broad signals at  $\delta 12-17$  (OH) and 8.56 (NH). The  $^{13}\text{C}$  NMR signals ( $\text{C}_\alpha$  at 170.64, two CN singlets at



**Form F.**

**Table 7.** *E*-Enol/*Z*-enol ratios and  $K_{\text{Enol}}$  values for systems **5/6**

System	<i>T</i> (K)	Solvent	Method	<i>E</i> -Enol (%)	<i>Z</i> -Enol (%)	Amide (%)	Ion (%)	<i>E</i> -Enol/ <i>Z</i> -enol	$K_{\text{Enol}}$	
<b>5a/6a</b>	298	CCl <sub>4</sub>	<sup>1</sup> H (OH, CH)	59		41			1.4	
			<sup>1</sup> H (OMe)	59		41		1.4		
			<sup>1</sup> H (NH)	57		43		1.3		
		CDCl <sub>3</sub>	<sup>1</sup> H (OH, CH)	9		91		0.1		
			<sup>1</sup> H (NH)	8		92		0.09		
			CD <sub>3</sub> CN	<sup>1</sup> H	Trace		>99		<0.01	
<b>5b/6b</b>	298	DMSO- <i>d</i> <sub>6</sub>	<sup>1</sup> H			100		<0.01		
			CCl <sub>4</sub>	<sup>1</sup> H (OH, CH)	65	26	9		2.6	10.1
			<sup>1</sup> H (NH)	64	25	11		2.6	8.1	
		CDCl <sub>3</sub>	<sup>1</sup> H (OMe)	65	26	9		2.6	10.1	
			<sup>19</sup> F	63	29	8		2.2	11.5	
			<sup>1</sup> H (OH, CH)	34	16	50		2.1	1	
			<sup>1</sup> H (NH)	34	15	51		2.3	0.96	
			<sup>1</sup> H (OMe)	35	15	50		2.3	1	
			<sup>19</sup> F	33	17	50		1.9	1	
		CD <sub>3</sub> CN	<sup>1</sup> H	Trace		>99		<0.01		
			<sup>19</sup> F			100		<0.01		
			<sup>1</sup> H	Trace		>99		<0.01		
		<b>5c/6c</b>	298	DMSO- <i>d</i> <sub>6</sub>	<sup>19</sup> F			100		<0.01
					<sup>1</sup> H			100		<0.01
					<sup>19</sup> F			100		<0.01
				CCl <sub>4</sub>	<sup>1</sup> H		100			>100
					<sup>19</sup> F		100			>100
					CDCl <sub>3</sub>	<sup>1</sup> H (OH, CH)		90	10	
CD <sub>3</sub> CN	<sup>1</sup> H (NH)				92	8		11.5		
	<sup>19</sup> F				92	8		11.5		
	<sup>1</sup> H (NH)				21	79		0.27		
	<sup>1</sup> H (OH, CH)				19	81		0.23		
	<sup>1</sup> H ( <i>i</i> -Pr-Me)				21	79		0.27		
	<sup>19</sup> F				24	76		0.32		
240	<sup>1</sup> H (NH)				27	73		0.36		
	<sup>1</sup> H (OH, CH)				26	74		0.35		
	<sup>1</sup> H ( <i>i</i> -Pr-Me)				27	73		0.36		
	<sup>19</sup> F				25	75		0.33		
	DMSO- <i>d</i> <sub>6</sub>			<sup>1</sup> H			100		<0.01	
				<sup>19</sup> F			100		<0.01	
<b>5d/6d</b>	298	CCl <sub>4</sub>	<sup>1</sup> H		100			>100		
			CDCl <sub>3</sub>	<sup>1</sup> H (NH)		98	2		49	
			<sup>1</sup> H (OMe)		98	2		49		
		CD <sub>3</sub> CN	<sup>1</sup> H ( <i>i</i> -Pr-Me)		95	5		45		
			<sup>1</sup> H		100			>100		
			<sup>1</sup> H (NH)		63	37		1.7		
			<sup>1</sup> H (OMe)		67	33		2		
			<sup>1</sup> H ( <i>i</i> -Pr-Me)		64	36		1.8		
			<sup>1</sup> H (NH)		81	19		4.3		
		240	<sup>1</sup> H (OH, CH)		81	19		4.3		
			<sup>1</sup> H (OMe)		81	19		4.3		
			<sup>1</sup> H ( <i>i</i> -Pr-Me)		79	21		3.8		
			DMF- <i>d</i> <sub>7</sub>	<sup>1</sup> H (NH), <sup>19</sup> F	23	64	13		0.36	6.7
				<sup>1</sup> H (NH), <sup>19</sup> F	24	59	17		0.4	4.9
				<sup>1</sup> H (NH), <sup>19</sup> F	21	59	20		0.36	4
		<sup>1</sup> H (NH), <sup>19</sup> F		19	57	24		0.3	3.2	
		<sup>1</sup> H (NH), <sup>19</sup> F		16	59	25		0.27	3	
		<sup>1</sup> H (NH), <sup>19</sup> F		16	56	28		0.28	2.6	
<sup>1</sup> H (NH), <sup>19</sup> F	15	55		30		0.27	2.3			
<sup>1</sup> H (NH), <sup>19</sup> F	12	56		32		0.21	2.1			
<sup>1</sup> H (NH), <sup>19</sup> F	8	57		35		0.14	1.9			
<sup>1</sup> H (NH), <sup>19</sup> F		63		37			1.7			
<b>5e/6e</b>	298	CDCl <sub>3</sub>	<sup>1</sup> H (NH), <sup>19</sup> F		61	39		1.6		
			<sup>1</sup> H (NH), <sup>19</sup> F		60	40		1.5		
			<sup>1</sup> H (NH), <sup>19</sup> F		57	43		1.3		
			<sup>1</sup> H (NH), <sup>19</sup> F		56	44		1.3		
			<sup>1</sup> H, <sup>19</sup> F		56	44		1.3		
			<sup>1</sup> H, <sup>19</sup> F		56	44		1.3		
			<sup>1</sup> H, <sup>19</sup> F		56	44		1.3		
			<sup>1</sup> H, <sup>19</sup> F		56	44		1.3		
			<sup>1</sup> H, <sup>19</sup> F		56	44		1.3		
			<sup>1</sup> H, <sup>19</sup> F		56	44		1.3		

Table 7. continued

System	<i>T</i> (K)	Solvent	Method	<i>E</i> -Enol (%)	<i>Z</i> -Enol (%)	Amide (%)	Ion (%)	<i>E</i> -Enol/ <i>Z</i> -enol	<i>K</i> <sub>Enol</sub>		
5f/6f	240	CD <sub>2</sub> Cl <sub>2</sub> CD <sub>3</sub> CN	<sup>1</sup> H, <sup>19</sup> F		100				>100		
	298		<sup>1</sup> H		100				>100		
	298		<sup>1</sup> H (NH)		83	17				4.9	
	240	DMF- <i>d</i> <sub>7</sub>	<sup>1</sup> H ( <i>i</i> -Pr-H)		83	17				4.9	
			<sup>1</sup> H ( <i>i</i> -Pr-Me)		86	13				6.6	
			<sup>19</sup> F		85	15				5.7	
			<sup>1</sup> H (NH)		91	6			0.06	15.7	
			<sup>19</sup> F		95	5				19	
			298	<sup>1</sup> H, <sup>19</sup> F					100		
			220	<sup>1</sup> H (NH)		29	71				
				<sup>1</sup> H ( <i>i</i> -Pr-H)		29	71				
				<sup>1</sup> H ( <i>i</i> -Pr-Me)		28	72				
			298	DMSO- <i>d</i> <sub>6</sub>	<sup>1</sup> H, <sup>19</sup> F				100		
			298	CDCl <sub>3</sub>	<sup>1</sup> H, <sup>19</sup> F		100				>100
			240	THF- <i>d</i> <sub>8</sub>	<sup>1</sup> H, <sup>19</sup> F	6	94				0.06
	180	<sup>1</sup> H (NH)	51		49				1.04	>100	
		<sup>1</sup> H [CH(CF <sub>3</sub> ) <sub>2</sub> ]	51		49				1.04	>100	
		<sup>1</sup> H ( <i>i</i> -Pr-H)	51		49				1.04	>100	
	190	<sup>1</sup> H (NH)	50		50				1	>100	
		<sup>1</sup> H [CH(CF <sub>3</sub> ) <sub>2</sub> ]	49.5		50.5				1	>100	
		<sup>1</sup> H ( <i>i</i> -Pr-H)	50		50				1	>100	
	200	<sup>1</sup> H (NH)	47		53				0.9	>100	
		<sup>1</sup> H (CH(CF <sub>3</sub> ) <sub>2</sub> )	47		53				0.9	>100	
		<sup>1</sup> H ( <i>i</i> -Pr-H)	46		54				0.85	>100	
	210	<sup>1</sup> H (NH)	41		59				0.69	>100	
		<sup>1</sup> H [CH(CF <sub>3</sub> ) <sub>2</sub> ]	44		56				0.78	>100	
		<sup>1</sup> H ( <i>i</i> -Pr-H)	43		57				0.75	>100	
	220	<sup>1</sup> H (NH)	38		62				0.61	>100	
		<sup>1</sup> H [CH(CF <sub>3</sub> ) <sub>2</sub> ]	40		60				0.67	>100	
		<sup>1</sup> H ( <i>i</i> -Pr-H)	39		61				0.64	>100	
230	<sup>1</sup> H (NH)	36	64					0.56	>100		
	<sup>1</sup> H [CH(CF <sub>3</sub> ) <sub>2</sub> ]	39	61					0.64	>100		
	<sup>1</sup> H ( <i>i</i> -Pr-H)	42	58				0.72	>100			
240	<sup>1</sup> H (NH)	35	65				0.54	>100			
	<sup>1</sup> H [CH(CF <sub>3</sub> ) <sub>2</sub> ]	37	63				0.59	>100			
298	CD <sub>3</sub> CN	<sup>1</sup> H, <sup>19</sup> F			100				>100		
298		<sup>1</sup> H (NH)		92	8				11.5		
240		<sup>1</sup> H (NH)	15	79	6			0.2	15.7		
5g/6g	298	DMF- <i>d</i> <sub>7</sub>	<sup>1</sup> H (NH, CH)			Trace	>99				
	220		<sup>1</sup> H (NH, CH)			Trace	>99				
	298		<sup>1</sup> H, <sup>19</sup> F				100				
	180	THF- <i>d</i> <sub>8</sub>	<sup>1</sup> H (NH)		96	4			24		
	190		<sup>1</sup> H (NH)		95	5			19		
	200		<sup>1</sup> H (NH)		92	8			11.5		
	210		<sup>1</sup> H (NH)		91	9			10		
	220		<sup>1</sup> H (NH)		88	12			7.3		
	230		<sup>1</sup> H (NH)		87	13			6.7		
	240		<sup>1</sup> H (NH)		83	17			4.9		
	250		<sup>1</sup> H (NH)		81	19			4.3		
	298		CD <sub>3</sub> CN	<sup>1</sup> H, <sup>19</sup> F				100		<0.01	
	240	<sup>1</sup> H, <sup>19</sup> F					100		<0.01		
	298	<sup>1</sup> H, <sup>19</sup> F						100			
	5h/6h	220	DMF- <i>d</i> <sub>7</sub>	<sup>1</sup> H, <sup>19</sup> F	100						
		298		<sup>1</sup> H, <sup>19</sup> F				100			
		298		<sup>1</sup> H, <sup>19</sup> F				100			
		298	DMSO- <i>d</i> <sub>6</sub>	<sup>1</sup> H		100				>100	
260		<sup>1</sup> H			100				>100		
298		<sup>1</sup> H			100				>100		
240		THF- <i>d</i> <sub>8</sub>	<sup>1</sup> H		100				>100		
180			<sup>1</sup> H		100				>100		
298			<sup>1</sup> H		100				>100		
240		CD <sub>3</sub> CN	<sup>1</sup> H		100				>100		
180			<sup>1</sup> H		100				>100		
298			<sup>1</sup> H		100				>100		
240	DMF- <i>d</i> <sub>7</sub>	<sup>1</sup> H		100				>100			
298		<sup>1</sup> H				100					
220		<sup>1</sup> H		100				>100			

Table 7. continued

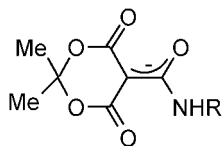
System	<i>T</i> (K)	Solvent	Method	<i>E</i> -Enol (%)	<i>Z</i> -Enol (%)	Amide (%)	Ion (%)	<i>E</i> -Enol/ <i>Z</i> -enol	<i>K</i> <sub>Enol</sub>
7	298	DMSO- <i>d</i> <sub>6</sub>	<sup>1</sup> H				100		
	298	CDCl <sub>3</sub>	<sup>1</sup> H		100				>100
	240		<sup>1</sup> H		100				>100
	298	CD <sub>3</sub> CN	<sup>1</sup> H	100					>100
	240		<sup>1</sup> H	100					>100
	298	DMF- <i>d</i> <sub>7</sub>	<sup>1</sup> H			100			
	220		<sup>1</sup> H	100					>100
	298	DMSO- <i>d</i> <sub>6</sub>	<sup>1</sup> H			100			
3c/4c	298	CD <sub>2</sub> Cl <sub>2</sub>	<sup>1</sup> H		<90	>10			<9

119.48 and 118.99, a =C<sub>β</sub> singlet at 34.85 and others; Table 5) are consistent with the enol structure **5g** at 220 K.

**The 5h/6h system.** In CDCl<sub>3</sub>, THF-*d*<sub>8</sub> and CD<sub>3</sub>CN. Enol **5h** was mostly the only observed product at 298 K or at lower temperatures. The <sup>1</sup>H NMR δ(OH) values are ca 15.03 in CDCl<sub>3</sub> and CD<sub>3</sub>CN and 15.41 ± 0.04 in THF-*d*<sub>8</sub>. Only in THF-*d*<sub>8</sub> were two additional signals with ca 7% of the intensity of the **5h** signals (assigned as **5h'** in Table 4) observed at 180 K at δ 11.63 and 9.28 but only one additional signal at δ 11.22 at 240 K or 10.82 at 298 K. On addition of Et<sub>3</sub>N to the THF-*d*<sub>8</sub> solution at 180 or 298 K the OH signal disappeared, and other signals shifted slightly. In a similar experiment in CD<sub>3</sub>CN the OH disappeared and the NH, CH and Me signals shifted upfield by ca 0.14 ppm.

The <sup>13</sup>C NMR data in CDCl<sub>3</sub> at 298 K are given in Table 5. The signals which appear in THF-*d*<sub>8</sub> at δ 170.71 (C<sub>α</sub>), 171.44, 164.26 (COO) and 73.39 shifted on addition of Et<sub>3</sub>N to δ 169.27, 166.74 and 77.32. In CD<sub>3</sub>CN the COO signals are not observed at rt, but at 240 K they are at 170.15, 163.57 (COO, vw), 168.76 and 73.32. On addition of Et<sub>3</sub>N at 298 K C<sub>α</sub> is at 167.78, COO at 166.10 and C<sub>β</sub> at 76.50. At 240 K the signals shift 0.2–0.8 ppm upfield.

In DMSO-*d*<sub>6</sub> and DMF-*d*<sub>7</sub>. In DMSO-*d*<sub>6</sub> at rt the <sup>1</sup>H and <sup>13</sup>C NMR shifts (Tables 4 and 5) are consistent with structure **5h**. In DMF-*d*<sub>7</sub> at 298 (220) K δ(OH) 15.68 (15.21) (br), δ(NH) 9.20 (9.27). On addition of Et<sub>3</sub>N the



**5h**: R = *i*-Pr

**7**: R = *t*-Bu

OH signal disappears, δ(NH) = 9.05 and the *i*-Pr and Me signals are shifted ca 0.2 ppm upfield. This is ascribed to the formation of ion **5h**<sup>-</sup>. The <sup>13</sup>C NMR signals at 298 K are at 169.98, 167.76 (C<sub>α</sub>, COO), 105.13 (CMe<sub>2</sub>), 73.30 (C<sub>β</sub>), 44.02 (*i*-Pr-CH), 25.99 (Me) and 23.40 (*i*-Pr-Me). On addition of Et<sub>3</sub>N they shift to δ 168.42, 166.48, 100.15, 77.34, 40.40, 26.13 and 23.40, i.e. CMe<sub>2</sub> and *i*-Pr-CH are shifted by 4–5 ppm upfield and C<sub>β</sub> is shifted by 4 ppm to lower field.

**System 7.** In CDCl<sub>3</sub> and CD<sub>3</sub>CN. Only the enol was observed according to the <sup>1</sup>H and <sup>13</sup>C NMR spectra (Tables 4 and 5), which are very similar in CDCl<sub>3</sub> and CD<sub>3</sub>CN.

In DMSO-*d*<sub>6</sub> and DMF-*d*<sub>7</sub>. Except for a very broad OH signal at rt the <sup>1</sup>H and <sup>13</sup>C spectra (Tables 4 and 5) resemble those in CDCl<sub>3</sub> and are ascribed to **7**. In DMSO-*d*<sub>6</sub> δ(O<sup>1</sup>H) 15.18, δ(N<sup>1</sup>H) 9.31 (br); δ<sup>13</sup>C 169.42 (C<sub>α</sub>), 166.72 (COO, br), 72.65 (C<sub>β</sub>). On addition of Et<sub>3</sub>N the OH signal is replaced by a very broad signal at 10.02 and the NH shift to δ 8.92; the δ(CH, CMe<sub>2</sub>) signals are shifted upfield by 0.24 and 0.15 ppm. The <sup>13</sup>C signals are shifted upfield by 2.23, 1.53, 5.19 (CMe<sub>2</sub>), -4.25(C<sub>β</sub>), 4.42(CMe<sub>3</sub>), -0.82 and -0.13 ppm, respectively.

In DMF-*d*<sub>7</sub> δ(OH) of 15.33 at 220 K further broadens on raising the temperature, and δ(OH) 15.42 (vb) at 298 K, whereas other δs are temperature independent. The <sup>13</sup>C NMR signals (Table 5) are consistent with structure **7**. On addition of Et<sub>3</sub>N at 298 K the OH signal disappears, probably owing to the formation of ion **7**<sup>-</sup>. Other signals shift 0.1–0.2 ppm upfield. However, at 220 K 7% of δ(OH) are still observed together with ca 80% of a signal at δ 10.65 which we ascribe to the solvated proton formed by ionization. The <sup>13</sup>C spectra at 298 and 220 K are similar and the main shifts compared with those of **7** are an upfield shift of 4.15 ppm for the CMe<sub>2</sub> and a downfield shift of 3.45 ppm for C<sub>β</sub>.

Product distributions of all the systems in all solvents are summarized in Table 7.



## DISCUSSION

### $K_{\text{Enol}}$ values

Table 7 contains an appreciable number of  $K_{\text{Enol}}$  values for the **5f/6** systems in  $\text{CCl}_4$ ,  $\text{CDCl}_3$ ,  $\text{THF-}d_8$ ,  $\text{CD}_3\text{CN}$ ,  $\text{DMSO-}d_6$  and  $\text{DMF-}d_7$  at several temperatures. These are valuable for comparison with the available data for the *N*-Ph analogs.

The decrease in the percentage of the enol, i.e.  $K_{\text{Enol}}$ , for any of the compounds at the same temperature is of the same order as found previously both for the *N*-Ph derivatives<sup>3d</sup> and the cyano ester substituted systems **3a-g/4a-g**,<sup>3d</sup> i.e.  $\text{CCl}_4 > \text{CDCl}_3 > \text{THF-}d_8 > \text{CD}_3\text{CN} > \text{DMSO-}d_6, \text{DMF-}d_7$ . However, there is no universal  $K_{\text{Enol}}$  (*N-i*-Pr)/ $K_{\text{Enol}}$  (*N*-Ph) ratio. In the majority of cases the  $K_{\text{Enol}}$  (*N-i*-Pr) system is higher by 1.3–11.3-fold than the  $K_{\text{Enol}}$  (*N*-Ph) system. Only in  $\text{CD}_3\text{CN}$  at 240 K is the  $K_{\text{Enol}}$  (*N-i*-Pr)/ $K_{\text{Enol}}$  (*N*-Ph) ratio 0.8. However, ratios based on  $K_{\text{Enol}}$  can exaggerate the difference since the corresponding percentages of the enol are 95% (in the **3f/4f** system) and 94% (in the **5f/6f** system), i.e. within the experimental error. The ratio for  $\text{CD}_3\text{CN}$  at 298 K, where the enol percentages are higher and the relative error is lower, favors the *N-i*-Pr enol. Finally, in  $\text{DMF-}d_7$  at 220 K **5e**, **5f** and **5g** are ionized at rt to  $\text{5e}^-$ ,  $\text{5f}^-$  and  $\text{5g}^-$ , but a large enol percentage is observed at 220 K. Data are not available for the *N*-Ph systems.

For the **5f/6f** system in  $\text{THF-}d_8$  both systems are completely enolic and for **5b/6b** in  $\text{CD}_3\text{CN}$  both systems are completely amidic and comparisons are not possible.

We conclude that the relative percentage of enol is generally somewhat higher for the *N-i*-Pr than for the *N*-Ph derivatives. However, in the narrow window in which the enol percentage can be measured, there is no case where only the *N-i*-Pr and no *N*-Ph enol is observed. The largest *N*-Ph  $\rightarrow$  *N-i*-Pr changes are for **5a/6a** in  $\text{CCl}_4$  (10%  $\rightarrow$  58%), for **5b/6b** in  $\text{CDCl}_3$  (24%  $\rightarrow$  50%), for **5c/6c** in  $\text{CD}_3\text{CN}$  (5%  $\rightarrow$  21%) and for **5e/6e** in  $\text{CD}_3\text{CN}$  (59%  $\rightarrow$  84%). These changes are not dramatic, and the hope that the *N*-Ph  $\rightarrow$  *N-i*-Pr change will enable one to obtain enols that are not observed in the *N*-Ph series is not fulfilled.

Plots of the limited data for  $K_{\text{Enol}}$  (*N*-Ph) vs  $K_{\text{Enol}}$  (*N-i*-Pr) values show linearity. In  $\text{CCl}_4$  the three-point plot has a slope of 0.32. In  $\text{CDCl}_3$  the four-point plot is linear with a slope of 2.1 and in  $\text{CD}_3\text{CN}$  the approximate three-point plot has a slope of 0.48.

Data on the effect of other *N*-alkyl groups are unavailable at present, but preliminary experiments with *N-t*-Bu systems suggest that the conclusion above is valid.

The higher enol content of the *N-i*-Pr systems is ascribed to the higher electron donation by the alkyl group compared with inductive electron withdrawal by the phenyl group which increases the contribution of resonance structure **2a** of the enol [Eqn(1)]. However,

caution should be exercised since the electronic effect will increase also the contribution of the amide resonance structure **1a**. The experimental data show that the former effect is more important, but discussion of small differences resulting from compensation of opposing effects on the two enols and the two amides seems unwarranted.

### Solvent effect on the $\delta(\text{OH})$ , $\delta(\text{NH})$ and $\delta(\text{CH})$ values

A benefit of the mostly higher  $K_{\text{Enol}}$  values for the *N-i*-Pr than for the *N*-Ph systems is that the enols are observed in solvents with higher dielectric constants than was previously possible. Consequently, we now have  $\delta(\text{OH})$  and  $\delta(\text{NH})$  values for the enols in  $\text{CCl}_4$ ,  $\text{CDCl}_3$ ,  $\text{THF-}d_8$ ,  $\text{CD}_3\text{CN}$  and  $\text{DMF-}d_7$  which enable us to generalize previous results and to explain an unclear result related to hydrogen bonding by these groups. Owing to solubility problems data are not available for all systems. The following generalizations emerge from the data in Table 4.

- The  $\delta(\text{OH})$  for a specific system increases with increase in polarity of the solvent. We noted previously<sup>3c</sup> that the  $\delta(\text{OH})$  value for the *N*-Ph systems in  $\text{CDCl}_3$  is ca 0.8 ppm higher than in  $\text{CCl}_4$ , but the reason was unclear. We find a similar difference of 0.7–0.8 ppm in the present work, a very small further increase of  $\delta(\text{OH})$  of 0.1–0.2 ppm in  $\text{CD}_3\text{CN}$  and practically no further increase in  $\text{DMF-}d_7$ . Exceptions are the lower  $\delta(\text{OH})$  for **5f** and **5g** in  $\text{CD}_3\text{CN}$  than in  $\text{CDCl}_3$ . Since the intramolecular hydrogen bond in **5a–h**, **7** is polar, it is expected to be affected by the solvent polarity, being more stabilized in a more polar higher dielectric solvent, as is observed. Since  $\delta(\text{OH})$  reflects the strength of the hydrogen bonds,<sup>7</sup> which eventually approaches a limit,  $\delta(\text{OH})$  is expected to reach a plateau at the higher dielectric constant solvent, as is indeed observed.
- The stronger is the hydrogen bond the higher should be  $\delta(\text{OH})$  in the same solvent. Comparison of  $\delta(\text{OH})$  for the symmetrical malonate esters **5a** and **5c** indicate that for **5a** with the stronger  $\text{O} \cdots \text{H} \cdots \text{O}=\text{C}-\text{OCH}_3$  hydrogen bond,  $\delta(\text{OH})$  in  $\text{CCl}_4$  is 15.59, whereas for **5c** with the weaker  $\text{O} \cdots \text{H} \cdots \text{O}=\text{C}-\text{OCH}_2\text{CF}_3$  bond (due to the electron withdrawal by the  $\text{CF}_3$  group),  $\delta(\text{OH})$  in  $\text{CCl}_4$  is 15.38. Similar results are found in the other solvents.

For **5b** the hydrogen bond can be either to a  $\text{CO}_2\text{Me}$  or to a  $\text{CO}_2\text{CH}_2\text{CF}_3$  and two  $\delta(\text{OH})$  values which are close to the values for **5a** and **5c**, respectively, are observed and ascribed to two geometric isomers. The higher value of 15.62 ppm is assigned to the *E*-isomer with *cis*  $\text{OH}/\text{CO}_2\text{Me}$  groups whereas the value of 14.60 ppm is assigned to the *Z*-isomer with *cis*  $\text{OH}/\text{CO}_2\text{CH}_2\text{CF}_3$  groups. This

is consistent with the isomer ratio ( $E/Z=2.6$ ), indicating a small effect of the non-hydrogen bonded ester group on the  $\delta(\text{OH})$  and hence on the bond strength. However, a complete analysis requires consideration of the hydrogen bonds to the NH group also (see below).

A similar analysis applies to the cyano ester enols **5d–f** where an intramolecular hydrogen bond to the OH is present only for the *Z*-isomer. At 298 K  $\delta(\text{OH})$  for *Z*-NCC(CO<sub>2</sub>R)=C(OH)NHPr-*i* are 14.81, 13.95 and 13.37 for R = Me, CH<sub>2</sub>CF<sub>3</sub> and CH(CF<sub>3</sub>)<sub>2</sub>, respectively, as expected from the weakening of the hydrogen bond on increasing the number of fluorine atoms. The trend is the same in CD<sub>3</sub>CN and in DMF-*d*<sub>7</sub>.

$\delta(\text{OH})$  is ca 1.5 ppm at a lower field for the symmetrical diesters **5a** and **5c** than for the corresponding cyanoesters *Z*-**5d** and *Z*-**5e**, respectively. This reflects an appreciable and similar reduction of the hydrogen bond strength by CN compared with CO<sub>2</sub>Me or CO<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>. Whereas CN is more electron withdrawing than either of the ester groups, the similar effect is surprising. It may be connected with moderation of the hydrogen bond to the NH due to electron withdrawal by the CO<sub>2</sub>R group, which has no counterpart with the CN.

In THF-*d*<sub>8</sub> the  $\Delta\delta(\text{OH}) = \delta(\text{OH}, E) - \delta(\text{OH}, Z)$  difference for **5f** of 1.6–2.2 is larger than for **5b** (0.9–1 ppm). This reflects the larger difference between the strengths of the intramolecular hydrogen bonds of the two EWGs.

- (c) A plot of  $\delta(\text{OH}, N\text{-Ph})$  vs  $\delta(\text{OH}, N\text{-}i\text{-Pr})$  (Fig. 4) for **5a–f, h** in CDCl<sub>3</sub> at 298 K is linear ( $R^2 = 0.9991$ ) with a slope of 1.15 with the following order of  $\delta(\text{OH})$  values for the **a** ~ **b** > **c** > **h** > **d** > **e** > **f** systems. This reflects quantitatively the trend discussed above and shows that the effects are identical in both systems.
- (d) By the  $\delta(\text{OH})$  criterion Meldrum's acid **5h** seems to have a weaker hydrogen bond than its open-chain analog **5a** despite its much higher  $K_{\text{Enol}}$  value. Consequently, while the hydrogen bond is a dominant factor in stabilizing the enols, other factors, e.g. the amide stability, also affect  $K_{\text{Enol}}$ , so that a high  $\delta(\text{OH})$  is not due only to a high  $K_{\text{Enol}}$  value.
- (e) The order of the  $\delta(\text{OH})$  values for system **5c** in various solvents is CCl<sub>4</sub> < CDCl<sub>3</sub> ≤ CD<sub>3</sub>CN for both the *N*-Ph and *N*-*i*-Pr systems.
- (f) The effect of the nitrogen substituent (Ph, *i*-Pr, *t*-Bu) on  $\delta(\text{OH})$  is small.
- (g) The temperature effect on  $\delta(\text{OH})$  is small over the range 58–78 °C, indicating an intramolecular hydrogen bond.
- (h) Most of the OH signals are sharp, but those observed for **5f** and **5g** in THF-*d*<sub>8</sub> at rt, for **5g** in DMF-*d*<sub>7</sub> and for **5h** in CD<sub>3</sub>CN are broad. Since cooling leads to sharpening of the signals, the broad signals are ascribed to an exchange process between the enol

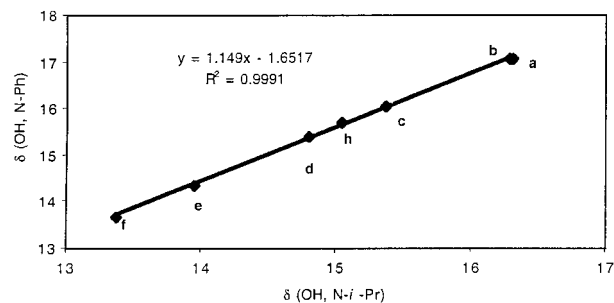


Figure 4. Plot of  $\delta(\text{OH}, N\text{-Ph})$  vs  $\delta(\text{OH}, N\text{-}i\text{-Pr})$  in CDCl<sub>3</sub> at 298 K

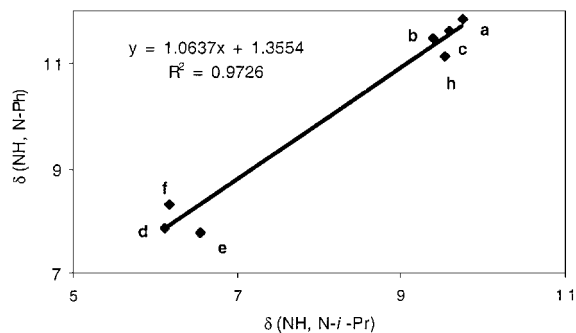


Figure 5. Plot of  $\delta(\text{NH}, N\text{-Ph})$  vs  $\delta(\text{NH}, N\text{-}i\text{-Pr})$  in CDCl<sub>3</sub> at 298 K

and either the amide or the enolate ion which is frozen on the NMR time-scale at the lower temperature.

- (i) The behavior of the  $\delta(\text{NH})$  signals resembles that of the  $\delta(\text{OH})$  signals, except that the effects are milder. A plot of  $\delta(\text{NH}, N\text{-Ph})$  vs  $\delta(\text{NH}, N\text{-}i\text{-Pr})$  for **5a–5f, h** in CDCl<sub>3</sub> (Fig. 5) is approximately linear ( $R^2 = 0.9726$ ) with a slope of 1.06. It differs from Fig. 4 since points **a, b, c** and **h** are grouped at the high  $\delta(\text{NH})$  region and points **d, e** and **f** are grouped at the lower  $\delta(\text{NH})$  region. As in Fig. 5,  $\delta(\text{NH})$  is higher in CD<sub>3</sub>CN and CDCl<sub>3</sub> than in CCl<sub>4</sub>. The relative stabilities of the *E*- and *Z*-isomers depends on the strengths of both the OH and NH hydrogen bonds. With the unsymmetrical substituted diesters **5b** the effects are in opposite directions and the strength of the OH hydrogen bonds dominates. The same applies also for the cyano esters, where only a hydrogen bond to the ester group occurs in the two isomers.
- (j) In the higher dielectric constant solvents ionization becomes important, especially for the more acidic systems (with more cyano groups or more fluorine atoms in the ester groups).

### E/Z enol ratios

There are only four (*E/Z*) *N*-*i*-Pr/(*E/Z*) *N*-Ph ratios (Table 8). The **5b/3b** ratios are close to unity since the dominant

**Table 8.** Ratios of  $K_{\text{Enol}}(N-i\text{-Pr})/K_{\text{Enol}}(N\text{-Ph})$  values and  $E/Z$ -enol ratios for  $N$ -*i*-Pr and  $N$ -Ph

System	Solvent	$T$ (K)	$K_{\text{Enol}}$		$K_{\text{Enol}}(N-i\text{-Pr})$	$E/Z$ -Enol		$E/Z(N-i\text{-Pr})$
			3/4	5/6	$K_{\text{Enol}}(N\text{-Ph})$	3/4	5/6	$E/Z(N\text{-Ph})$
<b>a</b>	CCl <sub>4</sub>	298	0.11	1.4	12.7			
	CDCl <sub>3</sub>	298	0.05	0.1	2			
<b>b</b>	CCl <sub>4</sub>	298	2.8	10.1	3.6	2.8	2.6	0.9
	CDCl <sub>3</sub>	298	0.3	1	3.3	2.8	2.3	0.8
<b>c</b>	CCl <sub>4</sub>	298	32	>100	>3.1			
	CDCl <sub>3</sub>	298	6.7	9	1.3			
	CD <sub>3</sub> CN	298	0.05	0.27	5.4			
<b>d</b>	CDCl <sub>3</sub>	298	>100	49	<0.5			
		240	>100	>100				
	CD <sub>3</sub> CN	298		1.7				
<b>e</b>	CD <sub>3</sub> CN	298	1.4	4.9	3.5			
<b>f</b>	THF- <i>d</i> <sub>8</sub>	298	>100	>100				
		240	49	>100	>2	1	0.56	0.56
	CD <sub>3</sub> CN	298	5.3	11.5	2.2	6		
		240	19	15.7	0.8	9	0.19	0.02

effect on the ratio is the hydrogen bond to the OH group and the effect of the weaker hydrogen bond to the NH group is smaller. The **5f/3f** ratios in THF-*d*<sub>8</sub> and CD<sub>3</sub>CN at 240 K are 0.6 and 0.02. This is due to the larger changes in the ratios for system **3** than for system **5**. The  $E/Z$  enol ratios in THF-*d*<sub>8</sub> for **3f** and **5f** do not differ much, presumably owing to H-bonding with the THF. In CD<sub>3</sub>CN, the ratio for **5f** is three-fold lower than in THF, whereas for **3f** it increases nine-fold. Comparison is difficult since different types of H-bonding to the two enols are involved in the three systems: Two intramolecular O...H—O bonds in the **b** system, mainly an O...H—O bond to the solvent in THF and mainly one intramolecular O...H—O bond in CD<sub>3</sub>CN.

### Temperature effect

THF-*d*<sub>8</sub> is a convenient solvent for measuring the temperature effects and enols/amide and  $Z$ -enol/ $E$ -enol ratios were determined in a wide temperature range for two systems. For the **5f/6f** system only the enols were observed (Table 7), and from 180 to 240 K the percentage

**Table 9.** Thermodynamic parameters for the **5g/6g** and **5d/6d** equilibration and the  $E/Z$ -enol isomerization of **5f** at 298 K

Parameter	<b>5g/6g</b> <sup>a</sup>	<b>5d/6d</b> <sup>b</sup>	$E/Z$ - <b>5f</b>
$\text{Ln}K_{\text{Enol}}^c$	0.66	0.64	1.07 <sup>d</sup>
$\Delta G^\circ$ (kcal mol <sup>-1</sup> )	-0.39	-0.38	-0.63
$\Delta H^\circ$ (kcal mol <sup>-1</sup> )	-2.32	-1.89	1.1
$\Delta S^\circ$ (cal mol <sup>-1</sup> K <sup>-1</sup> )	-6.48	-4.76	5.8

<sup>a</sup> In THF-*d*<sub>8</sub>.

<sup>b</sup> In DMF-*d*<sub>7</sub>.

<sup>c</sup>  $\text{Ln}K_{\text{Enol}}$  extrapolated from data for  $\text{Ln}K_{\text{Enol}}$  vs  $1/T$ .

<sup>d</sup>  $\text{Ln}K_i$  in THF-*d*<sub>8</sub>.

of **Z-5f** increased slowly but consistently from 49% to 64%, i.e. the  $Z$ -**5f**/ $E$ -**5f** ratio increased from 0.96 to 1.75. At 298 K only one enol was observed. The thermodynamic parameters are  $\Delta G^\circ = -0.6$  kcal mol<sup>-1</sup>,  $\Delta H^\circ = 1.1$  kcal mol<sup>-1</sup> and  $\Delta S^\circ = 5.8$  e.u. (Table 9) (1 kcal = 4.184 kJ). For the symmetrical **5g/6g** system only one enol is available, but the percentage of the observed amide increases from 4% at 180 K to 19% at 250 K. From the  $\log K_{\text{Enol}}$  vs  $1/T$  plot,  $\Delta G^\circ = -0.4$  kcal mol<sup>-1</sup>,  $\Delta H^\circ = -2.3$  kcal mol<sup>-1</sup> and  $\Delta S^\circ = -6.5$  e.u. (Tables 7 and 9).

The temperature effect on the two ratios for the **5d/6d** system was studied in DMF-*d*<sub>7</sub> between 220 and 350 K. The amide percentage increased with increase in temperature from 13% at 220 K to 44% to 350 K, giving  $\Delta G^\circ = -0.4$  kcal mol<sup>-1</sup>,  $\Delta H^\circ = -1.9$  kcal mol<sup>-1</sup> and  $\Delta S^\circ = -4.8$  e.u., values close to those in THF-*d*<sub>8</sub> (Table 9). In this system the  $Z$ -**5d**/ $E$ -**5d** ratio also changes from 2.8 at 220 K to 7 at 300 K, above which  $Z$ -**5d** is not observed. Consequently, the amide percentage roughly increases at the expense of the  $E$ -**5d** percentage.

In contrast, in CD<sub>3</sub>CN the amide percentage increased from 74% (240 K) to 79% (298 K) for **5c/6c**, from 19% (240 K) to 35% (298 K) for **5d/6d**, from 5.5% (240 K) to 16% (298 K) for **5e** and from 6% (240 K) to 8% (298 K) for **5f/6f**.

## EXPERIMENTAL

**General methods.** Melting-points and <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectra were measured as described previously. Solid-state <sup>13</sup>C NMR spectra were measured as described in Ref. 3c.

**Solvents and materials.** The deuterated solvents and the

**Table 10.** Analytical data for systems **5/6** and **7**

Compound <sup>a</sup>	Formula	M.p. (°C)	Calculated (%)			Found (%)		
			C	H	N	C	H	N
<b>6a</b>	C <sub>9</sub> H <sub>15</sub> NO <sub>5</sub>	93–94	49.76	6.96	6.45	49.90	7.09	6.70
<b>6b</b>	C <sub>10</sub> H <sub>14</sub> F <sub>3</sub> NO <sub>5</sub>	84–85	42.11	4.95	4.91	42.04	5.02	4.89
<b>5c</b>	C <sub>11</sub> H <sub>13</sub> F <sub>6</sub> NO <sub>5</sub>	86–87	38.95	3.86	4.13	38.95	3.77	3.81
<b>5d</b>	C <sub>8</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	117–119	52.16	6.57	15.21	52.46	6.65	15.26
<b>5e</b>	C <sub>9</sub> H <sub>11</sub> F <sub>3</sub> N <sub>2</sub> O <sub>3</sub>	151–152	42.86	4.40	11.10	43.18	4.63	11.25
<b>5f</b>	C <sub>10</sub> H <sub>10</sub> F <sub>6</sub> N <sub>2</sub> O <sub>3</sub>	124–126	37.51	3.15	8.75	37.77	3.30	8.68
<b>5g</b>	C <sub>7</sub> H <sub>9</sub> N <sub>3</sub> O	139–142	55.62	6.00	27.80	55.82	6.08	28.07
<b>5h</b>	C <sub>10</sub> H <sub>15</sub> NO <sub>5</sub>	98–100	52.38	6.59	6.11	52.17	6.52	6.14
<b>7</b>	C <sub>11</sub> H <sub>17</sub> NO <sub>5</sub>	108–110	54.31	7.04	5.76	54.21	6.96	5.80

<sup>a</sup> The structure of the solid tautomer is given.

starting materials were purchased from Aldrich and were used without further purification.

**Crystallographic data.** **6a.** C<sub>9</sub>H<sub>15</sub>NO<sub>5</sub>. Space group *P2<sub>1</sub>/c*; *a* = 14.251(5) Å, *b* = 14.229(6) Å, *c* = 17.158(4) Å,  $\beta$  = 91.16(2)°, *V* = 3478(2) Å<sup>3</sup>, *Z* = 12,  $\rho_{\text{calcd}}$  = 1.24 g cm<sup>-3</sup>.  $\mu$ (Cu K $\alpha$ ) = 8.69 cm<sup>-1</sup>, No. of unique reflections = 6457, No. of reflections with *I*  $\geq$  3 $\sigma$ <sub>*I*</sub> = 4817, *R* = 0.066, *R*<sub>w</sub> = 0.085. **5d:** C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>. Space group *P2<sub>1</sub>/n*; *a* = 17.742(3) Å, *b* = 10.231(2) Å, *c* = 5.491(1) Å,  $\beta$  = 96.70(2)°, *V* = 989.3(5) Å<sup>3</sup>, *Z* = 4,  $\rho_{\text{calcd}}$  = 1.24 g cm<sup>-3</sup>,  $\mu$ (Mo K $\alpha$ ) = 0.95 cm<sup>-1</sup>, No. of unique reflections = 1236, No. of reflections with *I*  $\geq$  2 $\sigma$ <sub>*I*</sub> = 720, *R* = 0.082, *R*<sub>w</sub> = 0.098. **5h:** C<sub>10</sub>H<sub>15</sub>NO<sub>5</sub>. Space group *P* $\bar{1}$ ; *a* = 9.235(1) Å, *b* = 9.720(2) Å, *c* = 7.320(1) Å,  $\alpha$  = 92.85(1)°,  $\beta$  = 110.48(1)°,  $\gamma$  = 70.74(1)°, *V* = 579.5(2) Å<sup>3</sup>, *Z* = 2,  $\rho_{\text{calcd}}$  = 1.312 g cm<sup>-3</sup>,  $\mu$ (Mo K $\alpha$ ) = 1.06 cm<sup>-1</sup>, No. of unique reflections = 1838, No. of reflections with *I*  $\geq$  2 $\sigma$ <sub>*I*</sub> = 1360, *R* = 0.078, *R*<sub>w</sub> = 0.099.

**Dimethyl *N*-isopropylcarboxamidomalonate (6a).** To dimethyl malonate (2.64 g, 20 mmol) in diethyl ether (10 ml) a dispersion of sodium (0.46 g, 20 mmol) in dry diethyl ether (50 ml) was added during 1 h with stirring. Stirring was continued for 24 h during which dry diethyl ether (40 ml) was added to the mixture. Isopropyl isocyanate (1.70 g, 20 mmol) in dry diethyl ether (10 ml) was added dropwise to the stirred suspension during 30 min. Stirring was continued for 4 h at rt, then the mixture was refluxed for 2 h. After stirring overnight at rt, the salt formed was filtered, washed with diethyl ether, the solid was dissolved in DMF (10 ml) and the solution was poured into ice-cooled 2 N HCl (200 ml) with stirring. The product was extracted with EtOAc (150 ml) and the extract was washed with ice-cold water (100 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated under reduced pressure, leaving solid dimethyl *N*-isopropylcarboxamidomalonate (1.4 g, 32%). Crystallization from EtOAc–petroleum ether gave pure **6a** as a

white solid, m.p. 93–94°C. NMR data and analyses are given in Tables 4, 5 and 10.

**2,2,2-Trifluoroethyl methyl *N*-isopropylcarboxamidomalonate (6b).** To a dispersion of sodium (0.12 g, 5 mmol) in diethyl ether (30 ml) 2,2,2-trifluoroethyl methyl malonate (1 g, 5 mmol) in diethyl ether (10 ml) was added dropwise during 30 min. Stirring was continued for 24 h at rt and then isopropyl isocyanate (0.42 g, 5 mmol) in diethyl ether (10 ml) was added dropwise during 30 min. After additional stirring for 24 h at rt, refluxing for 90 min and cooling to rt, the sodium salt formed was filtered and washed with diethyl ether, giving 1.4 g (91%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 298K),  $\delta$  1.03 (6H, d, *J* = 6.6 Hz, Me), 3.44 (3H, s, MeO), 3.86 (1H, octet, *J* = 6.6 Hz, *i*-Pr-H), 4.46 (2H, q, *J* = 9.4 Hz, CH<sub>2</sub>CF<sub>3</sub>), 8.50 (1H, d, *J* = 6.3 Hz, NH). <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 298 K),  $\delta$  -73.28 (t, *J* = 8.3 Hz); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 298K),  $\delta$  23.38 (q, *J* = 125 Hz, *i*-Pr-Me), 39.29 (dm, *J*<sub>d</sub> = 138 Hz, *i*-Pr-CH), 49.39 (q, *J* = 144 Hz, MeO), 57.57 (tq, *J*<sub>t</sub> = 149 Hz, *J*<sub>q</sub> = 34 Hz, CH<sub>2</sub>CF<sub>3</sub>), 77.23 (s, C $\beta$ ), 124.44 (qt, *J*<sub>q</sub> = 278 Hz, CF<sub>3</sub>), 167.94 (s, CON), 168.78 (s, COO), 171.06 (s, COO).

The salt (1.40 g, 4.6 mmol) was dissolved in ice–water (10 ml) and filtered. Concentrated HCl (3 ml) was added dropwise with stirring to the filtrate and the white solid formed was filtered (0.9 g, 69%). Recrystallization from DMF–H<sub>2</sub>O gave fine needles of **6b**, m.p. 84–85°C. NMR data and analyses are given in Tables 4–6 and 10.

**Bis(2,2,2-trifluoroethyl) *N*-isopropylcarboxamidomalonate (5c).** To a stirred mixture of bis(2,2,2-trifluoroethyl) malonate (1.34 g, 5 mmol) and triethylamine (1.02 g, 10 mmol) in DMF (10 ml) isopropyl isocyanate (0.42 g, 5 mmol) was added and the mixture was stirred for 24 h at rt. The solution was poured into ice-cold 2 N HCl (200 ml) with stirring and the white precipitate was filtered, giving 1.6 g (90%) of the crude product. Crystallization from EtOAc–petroleum ether gave **5c** as a white solid, m.p. 86–87°C. NMR data and analyses are given in Tables 4–6 and 10.

*Methyl N-isopropylcarboxamido(cyano)acetate (5d)*. To a stirred mixture of methyl cyanoacetate (0.99 g, 10 mmol) and triethylamine (2.04 g, 20 mmol) in DMF (10 ml), isopropyl isocyanate (0.85 g, 10 mmol) was added and the mixture was stirred for 24 h at rt. The mixture was poured into ice-cold 2 N HCl (200 ml) with stirring, and the white solid (1.2 g, 65%) formed was filtered. Crystallization from EtOAc–petroleum ether gave white needles, m.p. 117–119 °C. NMR data and analyses are given in Tables 4, 5 and 10.

*2,2,2-Trifluoroethyl N-isopropylamido(cyano)acetate (5e)*. To a stirred mixture of 2,2,2-trifluoroethyl cyanoacetate (1.67 g, 10 ml) and triethylamine (2.04 g, 20 mmol) in DMF (10 ml) isopropyl isocyanate was added. The mixture was stirred for 24 h, then poured into ice-cold 2 N HCl (200 ml) giving 2.2 g (87%) of crude **5e**. Crystallization from EtOAc–petroleum ether gave fine needles, m.p. 151–152 °C. NMR data and analyses are given in Tables 4–6 and 10.

*1,1,1,3,3,3-Hexafluoroethyl N-isopropylcarboxamidomalonate (5f)*. A mixture of 1,1,1,3,3,3-hexafluoroisopropyl cyanoacetate (0.59 g, 2.5 mmol), triethylamine (0.51 g, 5 mmol) and isopropyl isocyanate (0.21 g, 2.5 mmol) in DMF (5 ml) was stirred for 2 h and then poured into 2 N HCl solution (50 ml) with stirring. The precipitate was filtered and dried in air to give a solid (0.2 g, 25%), m.p. 124–126 °C. NMR data and analyses are given in Tables 4–6 and 10.

*2,2-Dicyano-N-isopropylacetamide (5g)*. Isopropyl isocyanate (0.85 g, 10 mmol) was added to a mixture of malononitrile (0.66 g, 10 mmol) and triethylamine (2.04 g, 20 mmol) in DMF (10 ml). The mixture was stirred for 6 h, then poured into ice-cold 2 N HCl (200 ml) and the precipitate formed was filtered and washed with ice-cold water and dried in air. Crystallization from EtOAc–petroleum ether gave **5g** as a white solid, m.p. 139–142 °C. NMR data and analyses are given in Tables 4, 5 and 10.

*5-(N-isopropylamido) Meldrum's acid enol (5h)*. To a mixture of Meldrum's acid (1.44 g, 10 mmol) and triethylamine (2.02 g, 20 mmol) in DMF (7 ml), isopropyl isocyanate (0.85 g, 10 mmol) was added. The mixture was stirred at rt for 2 h, then poured into ice-cold 2 N HCl (50 ml) and the precipitated white solid was filtered and washed with ice-cold water, giving 0.5 g (22%) of **5h**, m.p. 98–100 °C (from EtOAc–petroleum ether). NMR data and analyses are given in Tables 4, 5 and 10.

*5-(N-t-butylamido) Meldrum's acid enol (7)*. A mixture

of Meldrum's acid (2.88 g, 20 mmol), Et<sub>3</sub>N (4.04 g, 40 mmol) and *t*-butyl isocyanate (1.98 g, 20 mmol) in DMF (10 ml) was stirred for 2 h at rt. Work-up as for **5h** above gave 0.27 g (5%) of **7**, m.p. 108–110 °C. NMR data and analyses are given in Tables 4, 5 and 10.

## Supplementary material

Tables S1–S15 of crystal structure analyses, bond lengths and angles, positional and thermal parameters and stereoviews of compounds **6a**, **5d** and **5h** have been deposited in the Cambridge Structural Database.

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