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Isomeric Solid Enols on Ring- and Amide-Carbonyls of Substituted 2-Carbanilido-1,3-indandiones

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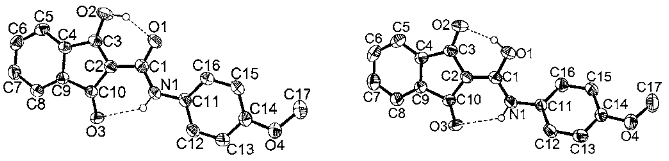
ABSTRACT

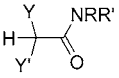


Keto enol

Amide enol

Both isomeric enols on ring carbonyl (5b) and on amide carbonyl (6b) derived from *N*-*p*-methoxyphenyl-2-carbamido-1,3-indandione (4b) were isolated, and their X-ray structures were determined. X-ray diffraction of the *N*-*o*,*p*-dimethoxy analogue indicated a disorder ascribed to the presence of a 6:4 mixture of 5c and 6c. Calculation (B3LYP/6-31+G*) gave good agreement with observed geometries. The calculated energies indicated that enols 6 are more stable by <1 kcal/mol than enols 5 and much more stable than amides 4.

Whereas enols of aldehydes and ketones are common, enols on the carbonyl groups of amides are scarce and were investigated only recently. They are observed in systems derived from the amides **1**, where Y,Y′ are electron-withdrawing, negative-charge-delocalizing substituents, and the enols **2** have a push−pull dipolar character (**2a**). Combinations of Y′ and Y groups studied so far are CO_2R, CO_2R'; CO_2R, RSO_2; CO_2R, CN; CN, CN; CO_2R, NO_2; CONHR, CN; CONHR, NO_2; and CN, CSNHR.[1]



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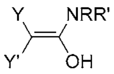

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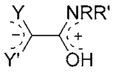

2a

According to calculations, the equilibrium constant $K_{enol} = [\mathbf{2}]/[\mathbf{1}]$ for the parent $CH_3COR'/CH_2{=}C(OH)R'$ system is many orders of magnitude higher for R′ = H, Me than for R′ = NHR.[2] This raises the possibility that in a competitive enolization on an amide carbonyl and on a ketone carbonyl when Y and Y′ = COR enolization will be exclusively on the latter. Likewise, when R′ = NHR and Y or Y′ = NO, enolization on the NO indeed gives the oxime.[3] In fact, when Y = COMe, Y′ = CO_2Et, enolization is on the carbonyl.[2b] However, in anthracyclines having the COCH(CONHR)CO moiety **3**, enolization on either the ring CO or the amido CO is known,[4] but both isomeric enols were never observed in one system.

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(2) Sklenak, S.; Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* **1998**, *120*, 10359.

(3) Williams, D. L. H.; Xia, L. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1429. The nitroso/oxime equilibria lie far on the oxime side (March, J. *Advanced Organic Chemistry, Reactions, Mechanisms and Structure*, 4th ed.; Wiley: New York, 1992; p 73).

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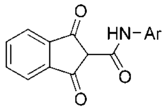
In a search for a system where a competitive enolization will favor the enol of the amide, we found that the 2-carbanilido-1,3-indandione system **4**, $X^1 = X^2 = H$, which a priori can give the amide **4**, the enol on a ring carbonyl **5**, the enol on the amide **6**, or a single minimum, where the hydrogen is bonded to both a ring and an amido oxygen **7**, gives exclusively, according to X-ray diffraction, the solid **6**, with internal hydrogen bonding to a ring CO.[5]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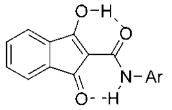
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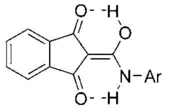
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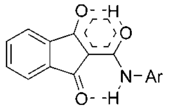
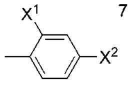

7

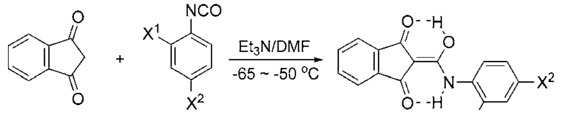
Ar =


a. $X^1 = X^2 = H$; **b**. $X^1 = H$, $X^2 = OMe$; **c**. $X^1 = X^2 = OMe$

The structural evidence in the solid state is of major importance for COCH(CONHR)CO systems. The important tool of C_β/H coupling which distinguishes enols **2** (no coupling) from amides **1** (large ^1J coupling) cannot distinguish between two enols such as **5** and **6**. Moreover, the methine hydrogen may be sufficiently acidic to ionize in polar media with a loss of the enol functionality.[6] Consequently, X-ray diffraction remains a strong and convincing tool for structure determination.

We found that the solid 4-methoxy ($X^1 = H$, $X^2 = MeO$), and 2,4-dimethoxy ($X^1 = X^2 = MeO$) derivatives display hitherto unobserved isomerism. Similarly to the preparation of enols of amides from aryl isocyanates with active methylene compounds,[1] reaction of 1,3-indandione with *p*-anisyl or 2,4-dimethoxyphenyl isocyanates with Et_3N at −65 to −50 °C in DMF gave products with a "formal" composition of amides **4** (eq 1).[7] The *p*-anisyl derivative was also prepared by reaction of 2-hydroxybenzoquinone with $PhI(OAc)_2$, followed by *p*-anisidine addition to the zwitterionic product.[8] The mps and ^1H NMR($CDCl_3$) spectra of the samples prepared by the two methods were nearly identical.

However, the sample obtained by eq 1 and crystallized from EtOAc displayed crystals with two colors: yellow and orange-red to red. The two types of crystals were separated by careful hand picking according to their color ("Pasteur's method"). Both crystals were suitable for X-ray diffraction and were found to be **5b** (the orange-red form, mp 149 °C) and **6b** (the yellow form, plates, mp 140−2 °C), respectively. It was found later that pure **5b** could be obtained by crystallization from EtOAc at 4 °C, whereas the remaining mother liquor gave **6b**, from THF at either 4 or −20 °C or from CH_2Cl_2 or CH_2Cl_2−petroleum ether at −20 °C. In contrast, **6b** was obtained once in a pure form from EtOAc at −20 °C and in another case as a **6b** + **5b** mixture, and as the major product, admixed with a little of **5b** from MeCN at 4 °C, or on cooling a solution in MeCN from 50 °C to room temperature. This is the first example when an enol on a keto carbonyl and an isomeric enol of amide were isolated in a single system. An example of solid isomers of amide and its enol was recently reported.[9]



$X^1 = H, OMe; X^2 = H, OMe$ (1)

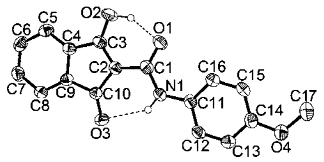


Figure 1. ORTEP drawing of **5b** (orange-red crystal).

The ORTEPs of **5b** and **6b** are given in Figures 1 and 2. Selected bond lengths and angles are given in Table 1. The full data are given in the Supporting Information. Solid **6b** displays two different conformations. In one (the top one in Figure 2), the methyl and the OH reside on the same side, and in the other one (bottom of Figure 2), they reside on the two sides, respectively. Both species are intermolecularly hydrogen bonded to one another.

The main identifying feature of **6b** is the C1−O1 former amide C−O bond length of 1.318 Å (1.313 Å in the other conformation), which is a normal C−O single bond length. The C1−C2 bond length of 1.403 (1.391) Å is longer than

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(4) (a) de C. T. Carrondo, M. A. A. F.; Matias, P. M.; Heggie, W.; Page, P. R. *Struct. Chem.* **1994**, *5*, 73. (b) Bordner, J. *Acta Crystallogr. Sect. B* **1979**, *35*, 219. (c) Glatz, B.; Helmchen, G.; Muxfeldt, H.; Porcher, H.; Prewo, R.; Senn, J.; Stezowski, J. J.; Stojda, R. J.; White, D. R. *J. Am. Chem. Soc.* **1979**, *101*, 2171.

(5) Mukhopadhyaya, J. K.; Rappoport, Z. Unpublished results. Although the X ray structure was unpublished, it was shown that **6a**/**7a** reacts with excess CH_2N_2 in ether to give exclusively 2-anilido-1,4-dimethoxynaphthalene by a sequence of reactions (Lei, Y. X.; Rappoport, Z. (*J. Org. Chem.* **2002**, *67*, 6971).

(6) For an example, see ref 1i.

(7) Song, J.; Rappoport, Z. 10th European Symposium on Organic Reactivity (ESOR 10), Roma, Italy, July 25−30, 2005, Abstract book p 46, Abs. IL 7. **Preparation: (a) 1,3-Dioxo-N-(*p*-methoxyphenyl)-2-indancarboxamide.** To a solution of 1,3-indandione (2 g, 13.7 mmol) in dry DMF (14 mL) at −65 to −50 °C was added Et_3N (3.84 mL, 13.7 mmol) with stirring for 5 min. 4-Methoxyphenyl isocyanate (2.04 g, 13.7 mmol) was then added and stirring continued for 1.5 h at the same temperature. The mixture was poured into ice-cooled 2 N HCl solution (20 mL 37% HCl + 80 g of ice), and the precipitate formed was filtered, washed with cold water, and dried in air to get 3.66 g (91%) of yellow powder, mp 143−4 °C (lit.[8] mp 140−3 °C). Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.59; N, 4.75. Found: C, 68.93; H, 4.59; N, 4.72. **(b) 1,3-Dioxo-*N*-(2,4-dimethoxyphenyl)-2-indancarboxamide.** The compound was prepared by a similar procedure to (a) above: orange powder; mp 188−190 °C. Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; N, 4.31. Found: C, 66.44; H, 4.68; N, 4.22. The NMR data of both species in solution is that of the enol of amide species (see text).

(8) Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M. *J. Org. Chem.* **2003**, *68*, 5627.

(9) Basheer, A.; Rappoport, Z. *Org. Lett.* **2006**, *8*, 5931.

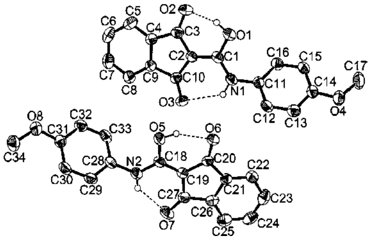

Figure 2. ORTEP drawing of **6b** (yellow crystal).

a normal C═C bond (1.368 Å).[10] This is consistent with the significant contribution of structure **2a** with a C1−C2 single bond character to the hybrid. The C2−C3 bond of 1.415 Å is slightly longer than C1−C2. These features resemble those of many other related enols of amides.[1] There are two hydrogen bonds with the O−H···O bond being stronger than the O−H···N bond (O···O and O···N nonbonding distances of 2.575 and 3.030 Å). The carbonyl group involved in the stronger hydrogen bond displays a longer bond than the other CO, as expected. Despite of the difficulty in locating an hydrogen in the X-ray diffraction, the O1-H bond of 0.87 Å is a normal O−H bond, and together with the O2···H bond of 1.74 Å (1.97 Å in the other conformer), exclude structure **7**.

In contrast, **5b** shows a shorter C1−O1 bond, although at 1.250 Å it is longer than a normal C═O bond, probably due to the involvement of O1 in the hydrogen bond. The C1−C2 bond length of 1.450 Å is reasonable for a Csp^2−Csp^2 bond, while the C2−C3 bond length of 1.368 Å is close to the expected C═C bond length and is significantly shorter than the other two C2−C bonds. C3−O2 is a single C−O bond at 1.304 Å, whereas C10═O3 is a normal C═O bond

Table 1. Selected Experimental and Calculated Crystal Data for **5b**, **6b** and **5c** + **6c**

A. Bond Length (Å)

	5b		**6b**		**5c** + **6c**			
bond	expt[a]	calcd	expt[a,b]	calcd	expt[c]	calcd		
C1−C2	1.450(3)	1.458	1.403(4) [1.391(4)]	1.403	1.431(3)	1.458[d]	1.404[e]	1.437[f]
C1−N1	1.343(2)	1.358	1.319(4) [1.321(4)]	1.339	1.332(2)	1.357[d]	1.338[e]	1.350[f]
C1−O1	1.250(2)	1.257	1.318(3) [1.313(3)]	1.327	1.278(2)	1.259[d]	1.328[e]	1.286[f]
C2−C3	1.368(3)	1.382	1.416(4) [1.426(4)]	1.438	1.386(2)	1.382[d]	1.438[e]	1.404[f]
C2−C10	1.464(2)	1.466	1.439(4) [1.432(4)]	1.447	1.457(2)	1.468[d]	1.449[e]	1.461[f]
C3−O2	1.304(2)	1.314	1.256(3) [1.234(3)]	1.248	1.292(2)	1.315[d]	1.249[e]	1.289[f]
C10−O3	1.218(2)	1.230	1.220(3) [1.228(3)]	1.239	1.221(2)	1.228[d]	1.236[e]	1.231[f]
C3−C4	1.475(3)	1.477	1.489(4) [1.496(4)]	1.497	1.479(2)	1.477[d]	1.497[e]	1.485[f]
C9−C10	1.504(3)	1.511	1.510(4) [1.504(4)]	1.505	1.507(2)	1.512[d]	1.507[e]	1.510[f]
O1−H	1.73(3)	1.723	0.87(4) [0.88(4)]	1.007	1.74(4)[d], 0.75(6)[e]	1.706[d]	1.008[e]	1.434[f]
O2−H	0.98(3)	1.011	1.74(4) [1.97(4)]	1.746	0.90(4)[d], 1.88(6)[e]	1.012[d]	1.726[e]	1.290[f]
O1−O2	2.622(2)	2.623	2.575(3) [2.753(3)]	2.655	2.5744(19)			
N1−H	0.86(2)	1.020	0.87(3) [0.84(3)]	1.025	0.85(2)	1.021[d]	1.026[e]	1.023[f]
O3−H	2.29(2)	2.106	2.39(3) [2.17(3)]	2.034	2.26(2)	2.167[d]	2.109[e]	2.144[f]
N1−O3	2.987(2)	2.952	3.030(3) [2.856(3)]	2.887	2.935(2)			

B. Bond Angle (deg)

angle	**5b**[a]	**6b**[a,b]	**5c** + **6c**[c]	**5c**[g]	**6c**[g]
N1C1O1	123.83(17)	117.8(3) [116.6(3)]	122.95(17)	124.4	119.3
N1C1C2	116.69(16)	123.5(3) [121.7(3)]	118.11(15)	116.5	121.3
O1C1C2	119.47(17)	118.7(3) [116.6(3)]	118.93(16)	119.0	119.4
C1C2C3	121.06(16)	121.0(3) [123.7(3)]	121.17(16)	121.0	122.0
C1C2C10	130.59(16)	129.0(3) [125.8(3)]	129.38(15)	130.7	127.7
C3C2C10	108.35(16)	110.3(3) [110.5(3)]	109.45(15)	108.3	110.3
O2C3C2	126.73(18)	125.8(3) [126.8(3)]	125.24(17)	125.9	126.0
O2C3C4	122.42(17)	126.8(3) [126.5(3)]	125.30(16)	123.3	127.2
C2C3C4	110.85(15)	107.4(3) [106.6(2)]	109.46(15)	110.8	106.7
C1O1H	101.1(10)	103(3) [107(2)]	109(4)		106.8
C1N1C11	130.09(16)	128.1(3) [127.6(3)]	129.89(15)	128.8	131.2
C1N1H	114.9(15)	116.1(19) [114(2)]	116.8(14)	115.6	113.3
C11N1H	115.0(15)	115.8(19) [118(2)]	113.2(14)	115.6	115.4
O1HO2	149(3)	159(4) [148(3)]	153(3)[d], 154(5)[e]	146.5	150.4
N1HO3	138.4(19)	130(2) [139(3)]	136.2(18)	135.7	135.3

[a] Measured at 295 K. [b] Values in square brackets correspond to the conformer at the bottom of Figure 2. [c] Measured at 173 K. [d] **5c**. [e] **6c**. [f] Values calculated on the basis of the equation: 61% **5c** +39% **6c** where **5c** and **6c** are the calculated bond lengths values of the species at B3LYP/6-31+G*. [g] Calculated values.

(1.218 Å). O2-H of 0.98 Å is a regular O−H bond and O1···H is a hydrogen bond at 1.73 Å. The O···O and O···N distances show a slightly weaker O−H···O bond than that in **6b**. The O−H···O hydrogen bonds are more bent than those for **6b**. The amido N−H is hydrogen bonded to the neighboring C10═O3 group.

X-ray diffraction of the 2,4-dimethoxy derivative displayed a disordered structure. For the enolic hydrogens two high-density locations were found and the spectra was analyzed as a mixture of the two isomers **5c** and **6c** in a ca. 6:4 ratio. This is corroborated also by the bond length of the “amide carbonyl”. The ORTEP drawings of both structures are shown in Figure 3, and selected bond lengths and angles are given in Table 1. The full data are in the Supporting Information.

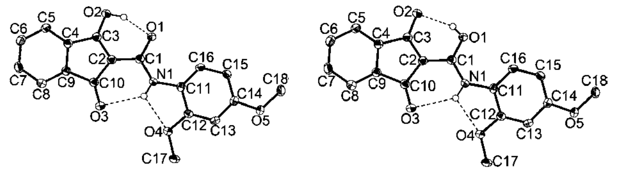

Figure 3. ORTEP drawing of a mixture of **5c** (61%, left) and **6c** (39%, right).

Despite the X-ray data which indicate an O−H···O bond of moderate strength, judged by the O···O nonbonded distances, the IR spectra of the solid **5b** and **6b** in nujol do not display a strong or medium O−H absorption. **6b** shows a weak signal at ca. 3250 cm^{-1} and **5b** shows a shoulder on the C−H signal at ca. 2700 cm^{-1}. The rest of the spectra down to 600 cm^{-1} are remarkably similar.[11]

Calculated Values. The structures, energies and gas phase acidities of **4a**−**c**, **5a**−**c**, and **6a**−**c** were calculated at B3LYP/6-31+G* (Table 2, Table S6 and Figure S1 in the Supporting Information). Crystal packing energies were not included in the calculation. The enol on ring **5** served as a reference. Negative values indicate a more stable species than **5** and vice versa. The three enols of amides **6** are the more stable species, by <1 kcal/mol than enols **5**. Hence, crystallization of either **5** or **6** alone or their separable (**5b**/**6b**) or unseparable (**5c**/**6c**) mixture is reasonable. Calculated barrier heights $\Delta H^{\ddagger}$ ($\Delta G^{\ddagger}$) in kcal/mol for the enols interconversions are very low: **5a** → **6a** 0.87 (1.48), **6a** → **5a** 0.49 (0.97), **5b** → **6b** 0.90 (1.57), **6b** → **5b** 0.20 (0.65), **5c** → **6c** 0.83 (1.57), **6c** → **5c** 0.06 (0.48). The amides **4** are significantly less stable than **5** or **6** and display four minima (**a** and **b**) and three minina (**c**).

Table 1 compares calculated with observed geometries of enols **5** and **6**. The agreement is good for the isolated derivatives **5b** and **5c**. For the 2,4-dimethoxy derivative, the calculated values based on a 61:39 ratio of **5c** and **6c** also give a good agreement with the crystallographic data of 6:4 ratio, with an average difference of 0.08 ± 0.05 Å for bonds which do not involve hydrogens.

Table 2. Relative Energies (kcal/mol) of **4**−**6a**−**c** Calculated at B3LYP/6-31+G*

species	E	H	G	ΔH_{acid}[a]	ΔG_{acid}[a]
4a-I[b]	8.97	8.54	5.61	309.8	304.7
5a	0.00	0.00	0.00	318.3	310.3
6a	−0.40	−0.38	−0.51	318.7	310.8
4b-I[b]	8.71	8.30	6.12	311.1	305.1
5b	0.00	0.00	0.00	319.4	311.2
6b	−0.78	−0.70	−0.92	320.1	312.2
4c-I[b]	7.47	7.17	4.60	315.4	309.8
5c	0.00	0.00	0.00	322.6	314.4
6c	−0.85	−0.77	−0.83	323.4	315.2

[a] Calculated acidities. *E* and *G* for H$^+$ are 1.48 and −6.28 kcal/mol, respectively. [b] Lowest *G* conformer.

The calculated structures for amides **4a**−**c-I** (Figure S1, Supporting Information) display normal C═O bond lengths of 1.215−1.228 Å and a rather long Csp^3−Csp^2 bond of 1.537 Å.

Attempted Isomerization. Attempted isomerization of solid **6b** to **5b** by irradiation with an Hg lamp did not result in an observable change.

Solid-State Cpmas ^{13}C NMR Spectra. A sample of **6b** display two molecules in the asymmetric unit of the crystal, reflected by doubling of most resonances. Quaternary and methyl resonances were observed in the Non-Quaternary and methyl Suppression (NQS) solid-state spectra. The seven quaternary carbon resonances resemble those from the CDCl$_3$ solution spectrum (given in parenthesis): 93.8/93.4 (95.3), 115.1 (128.2, NH−C (*ipso*-Ar)), 138.2 (137.7, O−C(*ipso*-Ar)), 157.0 (157.4), 164.5/163.4 (164.8), 190.5/187.3 (190.3) and 194.5/191.5 (193.1) ppm. In contrast, the crystals of **5b** give eight resonances at 100.7, 132.1, 134.5, 136.4, 155.1, 163.3, 186.6 and 189.7 ppm, which do not match those observed in CDCl$_3$. However, the observed ^{13}C NMR of **5b** in CDCl$_3$ resembles that of **6b** in CDCl$_3$ (Table S2 in the Supporting Information).

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Supporting Information Available: ^{1}H and ^{13}C spectra in solution, data for the calculations for **4**/**5**/**6a**−**c**, ^{13}C NMR data and IR spectra of solids **5b** and **6b**, and X-ray data for **5b**, **6b** and **5c**/**6c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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