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Keto–enol tautomerism of β-ketoamides and characterization of a sterically crowded α-amido-β-ketoamide

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epoc ABSTRACT: An α-amido-β-ketoamide (**1**) and two α-alkyl-β-ketoamides (**2** and **3**) were prepared and characterized, and their keto–enol tautomerism was studied by H/^{13}C NMR spectroscopy. Both α-alkyl-β-ketoamides **2** and **3** are in the keto form in $CDCl_3$, and their enol forms cannot be detected by ^{1}H/^{13}C NMR spectroscopy, whereas the α-amido-β-ketoamide **1** shows both keto and enol forms in $CDCl_3$ with an experimental K_E of 0.70 at 298 K. Copyright © 2002 John Wiley & Sons, Ltd.
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KEYWORDS: tautomerism; keto–enol; β-ketoamides

INTRODUCTION

Keto–enol equilibrium has been the subject of continuous interest in chemistry[1] and it has been studied by means of NMR,[2] HPLC,[3] kinetic methods,[4] Meyer's titration[5] and *ab initio* calculations.[6] The keto–enol equilibrium constant depends on the relative stability of the keto and enol forms, which can be affected by temperature, concentration of the substrates, solvent polarity and substituents on the substrates.[1] The tautomerism of simple ketones, β-diketones and β-keto esters has been well studied,[1–7] but little attention has been paid to that of β-ketoamides.[2c,4c]

α-Amido-β-ketoamides are known, but none of them has been characterized properly by NMR spectroscopy.[8] They have not been found to show both keto and enol forms.[8] The α-amido-β-ketoamide **1** was prepared in our laboratory by Ugi's multi-component reaction (MCR).[8a] It was found to show both keto and enol forms in $CDCl_3$, which made its ^{1}H and ^{13}C NMR spectra very complicated. In this work we characterized the tautomers. In addition, the substituent effect of the amido group on the keto–enol tautomerization of β-ketoamides is still unknown. Therefore, in this work we studied it and compared the difference in the substituent effects between the amido groups and the alkyl groups on the keto–enol tautomerism of β-ketoamides by NMR spectroscopy and *ab initio* calculations.

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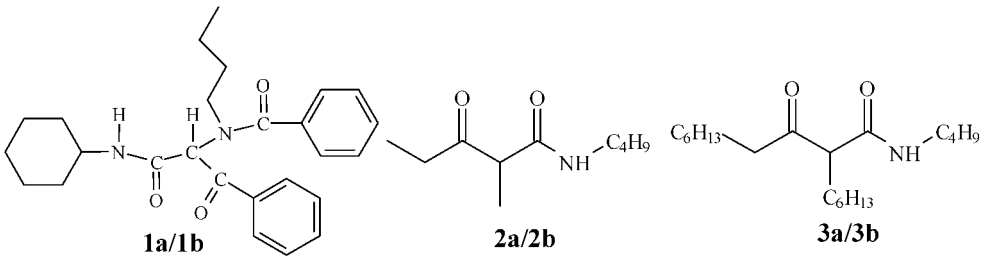
COMPUTATIONAL DETAILS

All the calculations reported here were performed with the Gaussian 98 program.[9] Geometry optimizations of **28a**, **29a** (keto form), **28b** and **29b** (enol form) were carried out at the HF/6–31+G* level in both the gas phase and a solvent ($\varepsilon = 4.81$) without any symmetry restriction. The Onsager self-consistent reaction field (SCRF) model[10] has been used to study systems in a solvent with a dielectric constant of 4.81, which is close to that of chloroform.[10b] The model treats the solvent as a continuum of uniform dielectric constant ε (the reaction field) and the solute is placed in a fixed spherical cavity of radius a_0 within the solvent. The radius a_0 of the cavity for each solute was evaluated based on its optimized structure in the gas phase. After all the geometry optimizations had been performed, analytic vibrational frequencies were calculated at the same level to determine the nature (minimum or saddle point) of the located stationary points. Thus all the stationary points found were properly characterized by evaluation of the harmonic frequencies. Single-point energies of the optimized structures of **28a**, **29a**, **28b** and **29b** were computed at the MP2/6–31+G* level in the solvent, and energies of all the stationary points were calculated at the same level with scaled zero-point vibrational energies included. The scaled factor of 0.8929 for zero-point vibrational energies was used according to the literature.[10b,11]

Thermal energies and entropies of stationary points were calculated at the HF/6–31+G* level in the solvent, and ΔH(298 K), ΔS(298 K) and ΔG(298 K) were calculated at the MP2/6–31+G*//HF/6–31+G* level in the solvent, as described by Jorgensen *et al.*[12]



a: keto form; **b**: enol form

RESULTS

According to Ugi's method,[8a] the α-amido-β-ketoamide **1** was prepared by a one-pot multi-component reaction (MCR) where cyclohexyl isocyanide, phenylglyoxal hydrate, n-butylamine and benzoic acid were mixed together in methanol at room temperature for 4 days. Single-crystal x-ray crystallography of **1** recrystallized from methanol showed that its structure is the enol form **1b** (Fig. 1). When **1** was dissolved in $CDCl_3$, both enol and keto forms of **1** appeared based on its ^1H and ^{13}C NMR spectra.

Structure assignment of **1** was done by x-ray crystallography, $^1H/^{13}C$ NMR (Fig. 2), COSY, NOESY and HMQC. According to both COSY and NOESY, ^1H NMR peaks at δ 3.08 and 3.94 are correlated with each other. Based on HMQC, the two peaks are correlated with the same carbon at δ 51.64. The splitting pattern of the two peaks is a doublet of triplets with coupling constants of 5.0 (d) and 12.5 (t) Hz. It is clear that the two peaks come from methylene protons adjacent to an N atom and the two protons are diastereotopic. Since the chemical shift difference of the two protons is fairly large (AX system), the two protons should be very close to a chiral center and

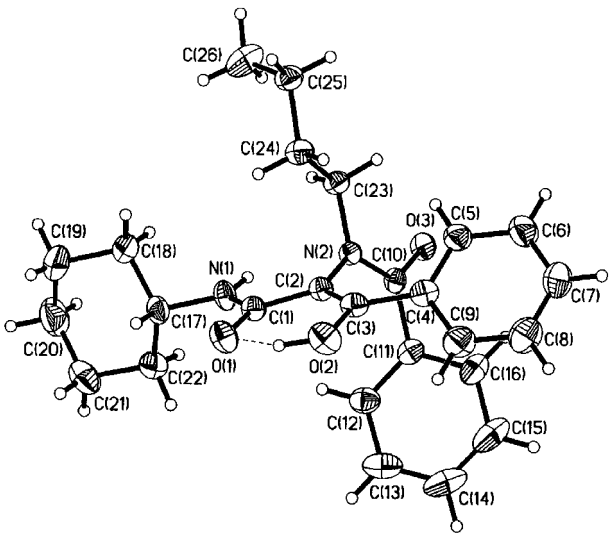
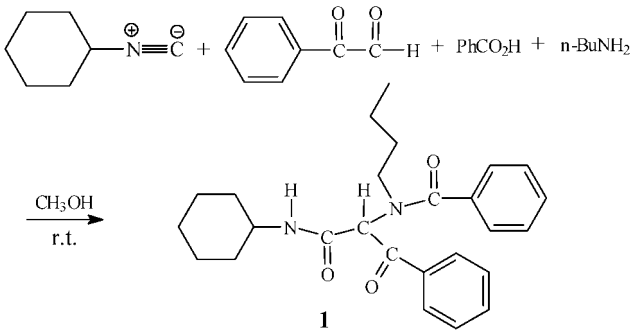


Figure 1. ORTEP diagram of **1b** with thermal ellipsoids drawn at the 30% probability level



a crowded structure makes rotation of the methylene protons slow, causing a significant difference in the electronic environment of the protons. Therefore, the methylene protons belong to the keto form **1a**. Similarly, based on the COSY spectrum, peaks at δ 3.38 and 3.48 in the ^1H NMR spectrum are correlated with each other. In the HMQC spectrum, the two peaks are correlated with the same carbon at δ 50.51. The splitting patterns of the two peaks are a multiplet but look like a doublet of triplets. The two peaks are also assigned to methylene protons adjacent to an N atom and the two protons are diastereotopic. Since the chemical shift difference of the two protons is fairly small (AB system), the two protons are not close to a chiral center and a less crowded structure makes rotation of the methylene protons slightly easier. Therefore, the methylene protons belong to the enol form **1b**. The above two kinds of methylene protons were used to monitor the [enol]/[keto] ratio for **1**.

Based on the above method, the K_E ([enol]/[keto]) value for **1** is 0.7 in $CDCl_3$ at 298 K. A $CDCl_3$ solution of **1** was heated under reflux overnight but its K_E value at 298 K changed very little, indicating that thermodynamic keto–enol equilibrium of **1** has been reached.

The singlet ^1H NMR peak at δ 5.89 is assigned to Cα-*H* of the keto form **1a** and its Cα appears at 67.85 ppm in the ^{13}C NMR spectrum. According to NOESY, the peak at δ 5.89 is correlated with one at δ 7.78, which is a doublet with a coupling constant of 7.3 Hz and is assigned N-*H* of the keto form **1a**. In the COSY spectrum, the N-*H* at 7.78 ppm is coupled with adjacent cyclohexyl C-*H* at δ 3.73 with the coupling constant of 7.3 Hz, because they are both three bonds apart and its dihedral angle is around

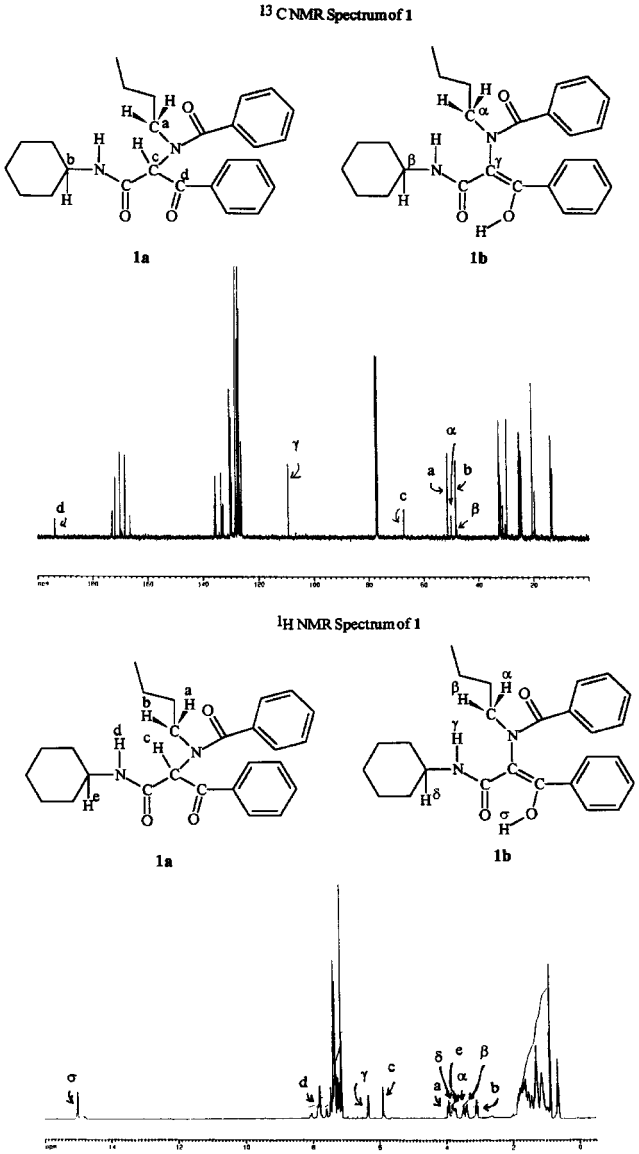


Figure 2. ^{1}H and ^{13}C NMR spectra of **1** in $CDCl_3$

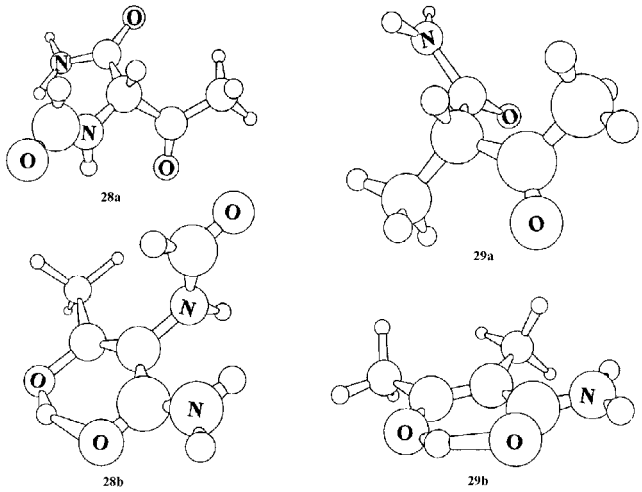


Figure 3. Optimized structures of **28a**, **28b**, **29a** and **29b** at HF/6–31+G* the level in a solvent with a dielectric constant of 4.81

180°. The correlation between Cα-*H* and N-*H* in NOESY indicates that they are *syn* to each other in **1a**.

The singlet ^{1}H NMR peak at δ 15.01 is assigned O-*H* of the enol form **1b** and its C(2) appears at δ 109.56 in the ^{13}C NMR spectrum. According to COSY, the N-*H* at δ 6.33 is coupled with adjacent cyclohexyl C-*H* at δ 3.83, $J = 8.36$ Hz, and they both belong to the enol form **1b**.

The α-alkyl-β-ketoamides **2** and **3** were prepared by treating ketene dimers with n-butylamine.[13b] When **2** and **3** were dissolved in $CDCl_3$, only keto forms could be detected in both cases based on their ^{1}H and ^{13}C NMR spectra.[13b]

Optimized structures of **28a**, **28b**, **29a** and **29b** are shown in Fig. 3. Based on the computational results [at the level of MP2/6–31+G*//HF/6–31+G* and in a solvent with a dielectric constant of 4.81, the energies, including ZPVE energy correction, of **28a**, **28b**, **29a** and **29b** are −528.89647, −528.89126, −399.82436 and −399.81633 hartree, respectively; ΔH(298 K), ΔS(298 K) and ΔG(298 K) of the enolization equilibrium of **28** are 3.59 kcal mol^{-1}, −5.19 cal mol^{-1} K^{-1} and 5.13 kcal mol^{-1}, respectively; ΔH(298 K), ΔS(298 K), and ΔG(298 K) of the enolization equilibrium of **29** are 5.56 kcal mol^{-1}, −3.66 cal mol^{-1} K^{-1} and 6.65 kcal mol^{-1}, respectively] at the MP2/6–31+G*// HF/6–31+G* level and in the solvent with a dielectric constant of 4.81, ΔG(298 K) of the enolization equilibrium of **28a** is 5.13 kcal mol^{-1}, (1 kcal = 4.184 kJ) i.e. the K_E(298 K) value of **28** is 0.00017, and ΔG(298 K) of the enolization equilibrium of **29a** is 6.65 kcal mol^{-1}, i.e. the K_E(298 K) value of **29** is 0.000013.

DISCUSSION

Several K_E values of β-keto esters and β-ketoamides are available and some of them are included in Table 1, but not all the data are directly comparable because they were measured by different methods and in different laboratories.[2cd,3a,4cd,7] Therefore, we compare only those data which have were obtained with the same method in the same laboratory.

Bunting and Kanter investigated the tautomerism of β-keto esters and β-ketoamides by means of their pH–rate profiles and found that the keto–enol equilibrium ratios are similar for β-keto esters and the corresponding β-ketoamides.[4c] Therefore, the electronic and steric effect of substituents on the keto and enol forms of the keto–enol equilibrium may be similar for β-keto esters and the corresponding β-ketoamides.

Brouillard and Dubois studied the keto–enol tautomerism of a series of six ethyl α-alkylacetoacetates (**4**–**9**) by means of kinetics of proton transfer reactions in aqueous

Table 1. K_E values for β-keto esters and β-ketoamides [R′C(O)CHRC(O)X]

No.	R′	R	X	K_E
1	C_6H_5	$N(n\text{-}C_4H_9)C(O)C_6H_5$	NHC_6H_{11}	0.7
2	C_2H_5	CH_5	$NH(n\text{-}C_4H_9)$	0
3	$n\text{-}C_7H_{15}$	$n\text{-}C_6H_{13}$	$NH(n\text{-}C_4H_9)$	0
4	CH_3	CH_5	OC_2H_5	0.0029[a] (0.05[d])
5	CH_3	C_2H_5	OC_2H_5	0.0017[a]
6	CH_3	$n\text{-}C_3H_7$	OC_2H_5	0.0013[a]
7	CH_3	$n\text{-}C_4H_9$	OC_2H_5	0.0009[a]
8	CH_3	$i\text{-}C_3H_7$	OC_2H_5	0.0005[a]
9	CH_3	$s\text{-}C_4H_9$	OC_2H_5	0.0004[a]
10	CH_3	H	OCH_3	0.08[b]
11	CH_3	H	OC_2H_5	0.087[b] (0.09[d])
12	C_6H_5	H	OCH_3	0.081[b]
13	CH_3	H	NH_2	0.11[b]
14	$4\text{-}[C_6H_4N^+CH_3]$	H	NH_2	0.18[b]
15	$4\text{-}[C_6H_4N^+CH_3]$	H	$N(CH_3)_2$	0.22[b]
16	CH_3	H	NHC_6H_5	0.02[c]
17	CH_3	H	$NHC_6H_4OCH_3$	0.005[c]
18	CH_3	H	$NHC_6H_4CO_2CH_3$	0.005[c]
19	CH_3	CH_2CHCH_2	NHC_6H_5	0.001[c]
20	CH_3	Cl	OC_2H_5	0.18[d]
21	CH_3	CN	OC_2H_5	13[d]
22	CH_3	CF_3	OC_2H_5	8.1[d]
23	C_6H_5	H	OC_2H_5	0.28[d]
24	CH_3	H	$O(n\text{-}C_4H_9)$	0.18[d]
25	CH_3	H	$O(t\text{-}C_4H_9)$	0.21[d]
26	CH_3	Cl	$O(n\text{-}C_4H_9)$	0.25[d]
27	CH_3	Cl	$O(t\text{-}C_4H_9)$	0.85[d]
28	CH_3	NHC(O)H	NH_2	0.00017[e]
29	CH_3	CH_3	NH_2	0.000013[e]

[a] Ref. 4d; the experiments were done by kinetic studies.
[b] Ref. 4c; the experiments were done by kinetic studies.
[c] Ref. 2c; the experiments were done by ^1H and ^{13}C NMR studies.
[d] Ref. 2d; the experiments were done by ^1H NMR studies.
[e] The experiments were done by *ab initio* calculations.

solution and found that K_E decreases as the number of α-alkyl carbon atoms increases and as the degree of branching of an α-alkyl substituent increases.[4d] There are two possible factors leading to this result: a steric effect on the enol or an electronic effect on the ketone. Because the ketone acidity pK_{CH} and enolization equilibrium constant pK_E have good linear relationships with Taft σ^* constants,[4d] they eliminated a steric effect interpretation but attributed the decrease in K_E to an electronic effect operating principally on the keto form, i.e. the $+I$ effect of alkyl groups would lead to an increase in thermodynamic stability of the ketones. By analogy with the ethyl α-alkylacetoacetates **4**–**9**, the α-allyl group of **19** stabilizes the keto forms by an electronic effect, and this makes its K_E smaller than that of **16**.[2c] Therefore, the very low K_E of **2** and **3** may be attributed to stabilization of the keto forms by an electronic effect of the α-alkyl groups.

Burdett and Rogers investigated the keto–enol tautomerism of a series of β-keto esters (**11**, **20–27**) by means of proton NMR spectroscopy and found that the K_E values of **11**, **20**, **21**, **22**, **24**, **26**, **25** and **27** increase as the σ-accepting ability of the α-substituent increases and this trend may be attributed to destabilization of the keto forms by the σ-accepting effect of the α-substituents.[2d] The amido substituent of **1a** and **1b** is a σ-acceptor since σ_1 of NHAc is 0.26 whereas the amido substituent is π-donor since σ_R of NHAc is -0.36.[14] Therefore, the phenomenon is expected to be seen in α-amido-β-ketoamides (**1**). According to the ^1H NMR spectrum of α-amido-β-ketoamide **1**, its K_E value is 0.7, which is high. It is possible that the σ-accepting effect of the α-amido group may destabilize the keto form (**1a**) more than the enol form (**1b**), resulting in an increase in enol content, because the σ-accepting effect of the amido substituent makes Cα of the keto form carry partial positive charge and the positive Cα is directly connected to two carbonyl carbons which also carry partial positive charge.

Su *et al.*[6f] reported that π-donor substituents such as NH_2, OH, F and Cl stabilize the enol forms of α-substituted acetaldehydes owing to the interaction between the lone-pair electrons of the substituents and the π^* orbital of the C=C bond of the enol forms. Therefore, if the lone-pair electrons of the amido substituent have any chance to interact with π^* orbital of the C=C bond of the enol form, the enol form **1b** would be stabilized. However, because the dihedral angle

C(10)—N(2)—C(2)—C(3) of **1b** is 71.3°, the enol form (**1b**) lacks of resonance stabilizing interaction between the lone-pair electrons of the amido nitrogen and the π* orbital of the C=C bond of the enol group. Therefore, this is not the reason why **1** has a high K_E. The same phenomenon can also be found in *ab initio*-optimized **28b** (Fig. 3), in which the amido group is also perpendicular to the sp^2-hybridized C=C plane of the enol group.

Even though the K_E values of **28** and **29** computed by *ab initio* calculations may be underestimated, it may be satisfactory to compare the results with each other using the same method. According to the computation results, the K_E value of **28** with an α-amido group is one order magnitude greater than that of **29** with an α-methyl group. As just mentioned, α-alkyl groups decrease the K_E values of β-keto esters and β-ketoamides by electronic stabilization of the keto forms. Therefore, the σ-accepting effect of α-amido group to increase the K_E values of β-ketoamides is limited. In addition to the electronic effect of the α-amido group, possibly there is another factor causing its high K_E value.

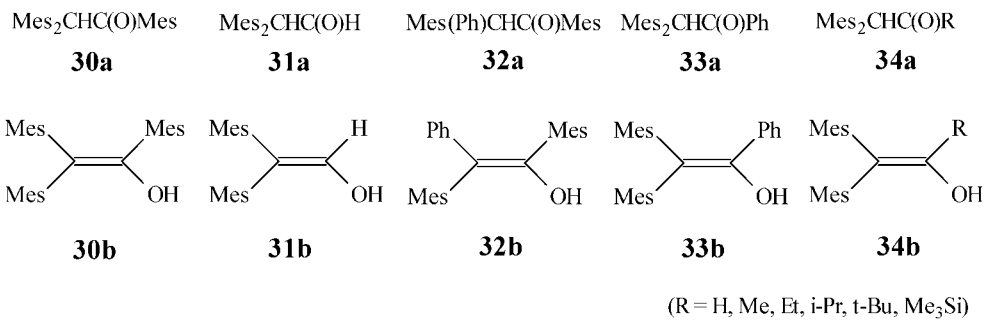
Brouillard and Dubois suggested that both the enol and enolate forms of β-keto esters are flat and they suffer from steric hindrance much less than the corresponding keto forms.[4d] Therefore, one may infer that destabilizing steric interactions caused by any of the substituents R′, R and X of β-keto esters and β-ketoamides may be much more significant in the keto form than those in the enol form.

Burdett and Rogers also found that the K_E values of β-keto esters (**10**, **11**, **24**, **25**, **26** and **27**) increase as the size of the alkoxyl group increases, and this may be attributed to steric interaction between the alkoxyl group and acetyl methyl group in the keto form.[2d] By analogy with the β-keto esters (**10**, **11**, **24**, **25**, **26** and **27**), bulky amide groups may also contribute to steric interaction with the substituent R′ on the carbonyl group in the keto form of β-ketoamides (**14** and **15**), and this leads to higher K_E values.[4c] The phenomenon may also be seen in α-amido-β-ketoamides (**1**). In the keto form **1a**, there are three bulky substituents attached to the sp^3-hybridized Cα and they are apart with an angle of ca 109°. On the other hand, the same three bulky substituents are attached on the sp^2-hybridized Cα in the enol form **1b** and they are apart with an angle of ca 120°. It seems that steric non-bonding interactions are more severe in the keto form **1a** than in the enol form **1b**, leading to destabilization of the keto form and a higher K_E value.

Fuson demonstrated that sterically hindered enols such as **30b**, **31b** and **32b** are isolable and stable if polystituted by bulky aryl groups such as a mesityl group, and he concluded that a necessary but not always sufficient condition to render the enols stable is their substitution by at least two bulky aryl groups.[15a] Later, the topic of sterically crowded stable simple enols received extensive attention.[15] After thermodynamic keto–enol equilibrium was reached, the K_E value of **30a/30b** was found to be 79 ± 7 at 353.6 K, whereas that of **33a/33b** was 1.02 ± 0.07 at 367.6 K.[15b] It seems that the higher K_E value is due to the steric bulk of the aryl substituents. However, Nugiel and Rappoport found that the K_E values at 353.6 K for the series **34a/34b** range from 20 ± 1 for R = H to 0.006 ± 0.0005 for R = *tert*-butyl and the corresponding ΔG values are linear with Taft's E_s constants with a slope of −1.5, indicating that the K_E values decrease rather than increase as the bulk of the α-alkyl substituent increases.[16] Therefore, Nugiel and Rappoport suggested that whereas the kinetic stability of the bulky simple enols is probably due mainly to steric hindrance in the formation of the transition states of ketonization, the relatively high thermodynamic stabilities of the enols are due to a complex interplay of polar, resonance, hyperconjugation, steric and hydrogen-bonding effects in both the enols and ketones.[15b]

CONCLUSIONS

The α-amido-β-ketoamide **1** was well characterized and consists of both enol and keto forms in $CDCl_3$ with a high K_E value of 0.7. The high K_E value may be due to both a destabilizing electronic effect of the amido group operating principally on the keto form and destabilizing steric non-bonding interactions in the keto form caused by three bulky substituents (R′, R and X). On the other hand, enol forms of **2** and **3** cannot be detected by proton NMR spectroscopy, i.e. the K_E values of **2** and **3** should be small, which is due to the stabilizing electronic effect of α-alkyl groups operating principally on the keto forms.



In other words, the bulky α-amido substituent makes α-H of the keto form **1a** much more acidic relative to the acidity of the enol form **1b**. However, the α-alkyl substituents make α-H of the keto forms (**2a**, **3a**) less acidic relative to the corresponding enol forms (**2b**, **3b**).

EXPERIMENTAL

General

Unless stated otherwise, reagents were obtained from commercial suppliers and used as received. NMR spectra were obtained using Bruker model 200 and 400 NMR spectrometers. High-resolution mass spectra were taken on a VG 70250S mass spectrometer. Cyclohexyl isocyanide[13a] and α-alkyl-β-ketoamides **2a** and **3a**[13b] are known and were prepared according to the literature methods.

Crystal structure refinement for 1b

The intensity data were collected on a Nonius Kappa CCD diffractometer using Mo Kα radiation ($\lambda = 0.71073$ Å) with an θ–ω scan at 293(±2) K. The unit cell parameters were determined by least-squares refinement on diffractometer angles $5.33 < \theta < 27.50°$ for 5432 reflections. The structure was solved by direct methods using SHELXS-97[17a] and refined by full-matrix least-squares on F^2 using the SHELXL-97 program.[17b]

Crystal data for 1b

$C_{26}H_{32}N_2O_3$, crystal size $0.50 \times 0.50 \times 0.50$ mm, $M = 420.54$ g mol^{-1}, triclinic, space group $P\bar{1}$, $a = 9.4778(1)$ Å, $b = 11.3857(2)$ Å, $c = 12.2832(2)$ Å, $\alpha = 82.673(1)°$, $\beta = 79.617(1)°$, $\gamma = 65.572(1)°$, $V = 1185.00(3)$ Å^3, $Z = 2$, $D_{calc} = 1.179$ g cm^{-1}, $F(000)$ 452, $\mu = 0.077$ mm^{-1}. The final R indices were $R_1 = 0.0516$, $wR_2 = 0.1341$. The goodness-of-fit on F^2 was 1.046. Crystallographic data for crystal **1b** have been deposited at the Cambridge Crystallographic Data Center as CCDC 173897.

Preparation of α-amido-β-ketoamide 1

Phenylglyoxal hydrate (0.122 g, 0.9 mmol) was added to a solution of n-butylamine (0.076 g, 0.9 mmol) in methanol (5 ml). The solution was stirred for 20 min at room temperature. Cyclohexyl isocyanide (0.1 g, 0.9 mmol) and benzoic acid (0.111 g, 0.9 mmol) were added to the solution and the mixture was stirred at room temperature for 4 days until a white solid precipitated. After filtration, the precipitate was washed with methanol and recrystallized from methanol to give **1** (0.203 g, 4.8 mmol) in 54% yield. ^{1}H NMR ($CDCl_3$), δ 0.62–1.83 (*m*, $CH_3CH_2CH_2$—CH_2N— and methylene protons of cyclohexyl groups for enol/keto forms), 3.08 (1H, d of t, —HC*H*N— of the keto form **1a**), 3.39 (1H, m, —HC*H*N— of the enol form **1b**), 3.48 (1H, m, —*H*CHN— of the enol form **1b**), 3.73 (1H, m, —C*H*N— of the *N*-cyclohexyl group of the keto form **1a**), 3.81 (1H, m, —C*H*N— of the *N*-cyclohexyl group of the enol form **1b**), 3.94 (1H, d of t, —*H*CHN— of the keto form **1a**), 5.89 (1H, s, *H*Cα of keto form **1a**), 6.33 (1H, d, *H*N— of the enol form **1b**), 7.13–7.46 (m, Ph*H* for enol/keto forms), 7.79 (1H, d, *H*N— of the keto form **1a**), 15.01 (1H, s, —O*H* of the enol form **1b**). ^{13}C NMR ($CDCl_3$), δ 13.28, 13.73, 19.65, 20.51, 24.44, 24.65, 24.76, 25.21, 25.40, 30.02, 31.19, 31.65, 32.10, 32.36, 32.71, 32.74, 47.93, 48.32, 50.51, 51.64 (alkyl carbons of enol/keto forms), 67.85 (Cα of keto form **1a**), 109.56 (C-2 of enol form **1b**), 126.06, 126.16, 126.59, 126.75, 126.90, 127.25, 127.39, 127.52, 127.59, 127.74, 128.12, 128.23, 128.26, 128.30, 128.46, 129.62, 129.74, 129.92, 130.28, 132.75, 133.44, 135.40, 135.54, 135.84 (phenyl carbons of enol/keto forms), 166.55, 168.20, 170.10, 171.74, 172.98 (amide carbons and enol carbon of enol/keto forms), 192.89 (ketone carbon of keto form **1a**) ppm. HRMS (EI) for $C_{26}H_{32}N_2O_3$, *m/z* calcd 420.24129, found 420.24150.

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Supplementary material

Three figures showing COSY, NOESY and HMQC of **1b** are available at the epoc website at http://www.wiley.com/epoc.

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