DOI: 10.1002/ejoc.201001451

Electron-Deficient Aryl β-Diketones: Synthesis and Novel Tautomeric Preferences

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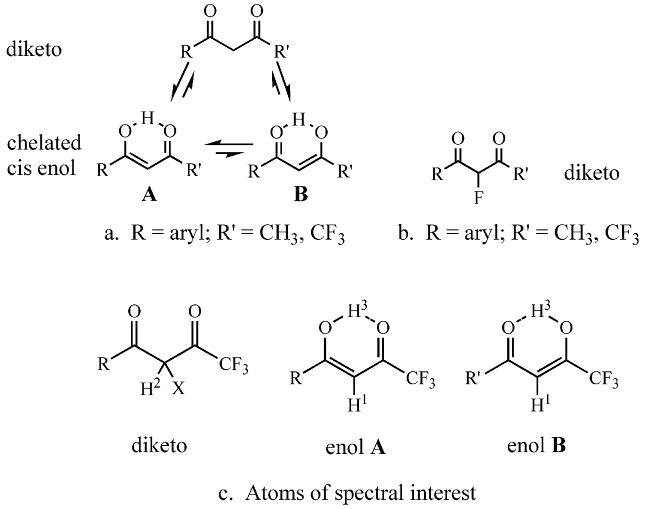
Keywords: Ketones / Enols / Tautomerism / Keto–enol equilibrium / 1,3-Diketones

Fluorinated aryl β-diketones were prepared using Claisen and electrophilic fluorination methods. The keto–enol and enol–enol tautomerism of these compounds were examined in the solid state, as neat liquids and in polar, aprotic solution by crystallography and spectroscopy. Neat-liquid spectroscopic measurements as well as single crystal X-ray crystallographic results for selected electron-deficient aryl β-diketones suggest a single, chelated *cis*-enol isomer that is conjugated with the aryl ring. In polar aprotic solvents, nonfluorinated aryl β-diketones equilibrate rapidly from the chelated *cis*-enol form to a tautomeric mixture of *cis*-chelated enol and a substantial proportion of the diketone form, trifluoromethylated aryl β-diketones show only limited equilibration from the chelated *cis*-enol to the diketone form, with 2-fluoro-1-aryl β-diketones again displaying only the diketonic form.

Introduction

Keto–enol tautomerism in trifluoromethyl β-diketones has been studied extensively in solution.[1–8] Scheme 1 depicts the principal tautomeric structures for nonfluorinated and trifluoromethylated β-diketones (frame a), 2-fluoro β-diketones (frame b) and atoms of spectral interest in this study (frame c). Table 1 lists spectroscopic indicators for the various tautomers.[1–5,7–9]

Prior researchers have probed the keto–enol and enol–enol equilibria of various trifluoromethylated and nonfluorinated aryl β-diketones using computational methods and experimentally in non-polar and polar media.[1,2,5–9] Ab initio calculations confirm a general thermodynamic stability trend: chelated *cis*-enol **A** > chelated *cis*-enol **B** > diketo form in the gas phase as well as in non-polar and polar, protic solvents.[1,2] In general, while solution state NMR spectroscopic studies can easily distinguish between the diketo and enol tautomers of β-diketones, resolution of the enol tautomeric forms has remained contentious. Enol–enol equilibria in aryl trifluoromethyl β-diketones, for example, have been estimated using a combination of NMR chemical shift arguments, model compounds and ^{13}C-^{19}F coupling constants; the results, however, are often ambiguous. These studies have generally concluded that most aryl β-diketones exist as near-unity mixtures of *cis*-chelated enol forms **a** and



a. R = aryl; R' = CH_3, CF_3

b. R = aryl; R' = CH_3, CF_3

c. Atoms of spectral interest

Scheme 1. β-Diketone tautomeric species of interest.

Table 1. Spectral information for trifluoromethyl β-diketones.

Method	Units	R	Diketo form	Enol **A**	Enol **B**
^1H NMR	δ / ppm	aryl	X = H; H^2: 3.9–5.0 X = F; H^2: 5.5–6.5	H^1 5–7 H^3: 13–18	H^1 5–7 H^3: 13–18
Raman/IR	$\tilde{\nu}$ / cm^{-1}	aryl	1685–1700 1700–1780	1595–1620	1650–1680

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001451.

b in nonpolar and slightly polar solvents.[5] The diketo tautomer and other nonchelated enol forms, when observed, are present in small proportions.

However, this equilibrium shifts toward the diketo form in solvents like ethanol rapidly, appears to be concentration dependent and leads to acetal formation over extended periods.[1] The limited studies conducted in polar aprotic solvents show a shift in equilibrium toward the diketo form for non-fluorinated aryl β-diketones whereas trifluoromethyl aryl β-diketones and aryl 2-fluoro β-diketones give hydrates over extended periods.[5,6]

Infrared spectroscopy has also been used to identify the presence of specific tautomeric forms of nonfluorinated aryl β-diketones in solution. Studies of benzoylacetone derivatives conducted by Lowe and Ferguson confirm a marked preference for enol form **A**, pointing to characteristic infrared bands (Table 1) that differentiate the tautomers.[7] Complementary Raman investigations have not been reported.

Solid-state investigations of this phenomenon are sparse. While examining benzoylacetone's enol–enol equilibrium by neutron diffraction, Madsen and co-workers found that the enol proton occupied a "centered" location between the two oxygens,[10] implying the possibility of a *cis*-enolic equilibrium in the solid state. Vila's group also posited a dynamic enol–enol equilibrium for benzoylacetone based on ^{13}C CPMAS and solution state NMR spectroscopic studies.[11] Neat liquid investigations have likewise received little attention in the literature.

Our efforts address these experimental gaps with a systematic, comparative study of fluorinated aryl β-diketone enol–enol and keto–enol equilibria in the solid-state, as neat liquids and in polar, aprotic media. A combination of crystallographic, Raman, infrared, and NMR methods allow determination of whether discreet tautomeric forms may be identified.

Results and Discussion

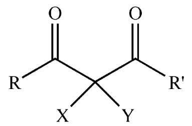
β-Diketone Synthesis

Figure 1 shows the β-diketones investigated in this study. Compounds **1a** and **1d** are commercially available; **1b**, **1c**, **2a**, **2b**, **2d**, **2e** were prepared by literature methods,[1,4,12–14] while **2c** and **3b** were prepared by via Scheme 2.

Solid-State/Neat-Liquid Studies

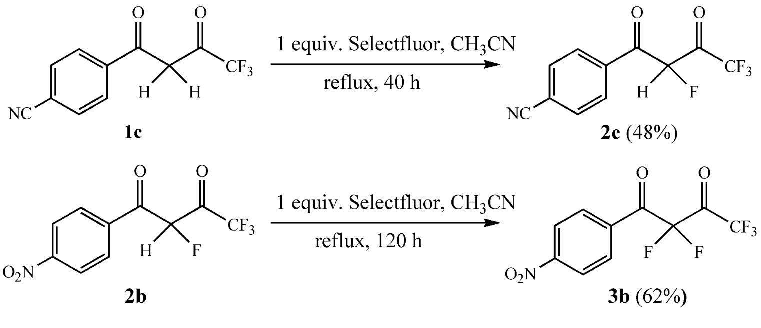
Solid-state experiments were performed on all molecules, and in instances where the solids had melting points below 70 °C, neat liquid studies were also conducted. Compelling evidence for preferential tautomerization toward chelated *cis*-enol **A** was found in the case of 4,4,4-trifluoro-1-(4-nitrophenyl)-1,3-butanedione (**1b**) where a crystal structure was obtained from X-ray quality crystals. The ORTEP diagram is shown in Figure 2 and measurements are compared to those reported by Madsen for **1d** in Table 2.

Key differences are noted in our X-ray results when compared to the neutron diffraction data of Madsen and co-workers. The C^7–C^8 and C^9–O^4 bond lengths for **1b** show a higher degree of double bond character than those of **1d**



1a: R = Ph, R' = CF$_3$, X = Y = H; **2a**: R = Ph, R' = CF$_3$, X = F, Y = H;
1b: R = 4-NO$_2$Ph, R' = CF$_3$, X = Y = H; **2b**: R = 4-NO$_2$Ph, R' = CF$_3$, X = F, Y = H;
3b: R = 4-NO$_2$Ph, R' = CF$_3$, X =Y=F; **1c**: R = 4-NCPh, R' = CF$_3$, X = Y = H;
2c: R = 4-NCPh, R' = CF$_3$, X = F, Y = H; **1d**: R = Ph, R' = CH$_3$, X = Y = H;
2d: R = Ph, R' = CH$_3$, X = F, Y = H; **2e**: R = 4-NO$_2$Ph, R' = CH$_3$, X = F, Y = H

Figure 1. β-Diketones investigated.



Scheme 2. Diketone synthesis.

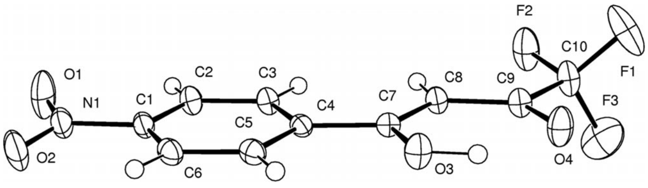


Figure 2. ORTEP drawing of **1b** depicting ellipsoids at the 50% probability level and hydrogen atoms drawn with arbitrary radii for clarity.

Table 2. Selected interatomic distances and bond lengths of **1b** and **1d**.

	Interatomic distances/bond length / Å O^3–O^4	C^7–O^3	O^3–H	C^9–O^4	C^7–C^8	C^8–C^9
1b	2.553	1.317	0.96	1.243	1.378	1.413
1d	2.498	1.293	1.245	1.286	1.405	1.414

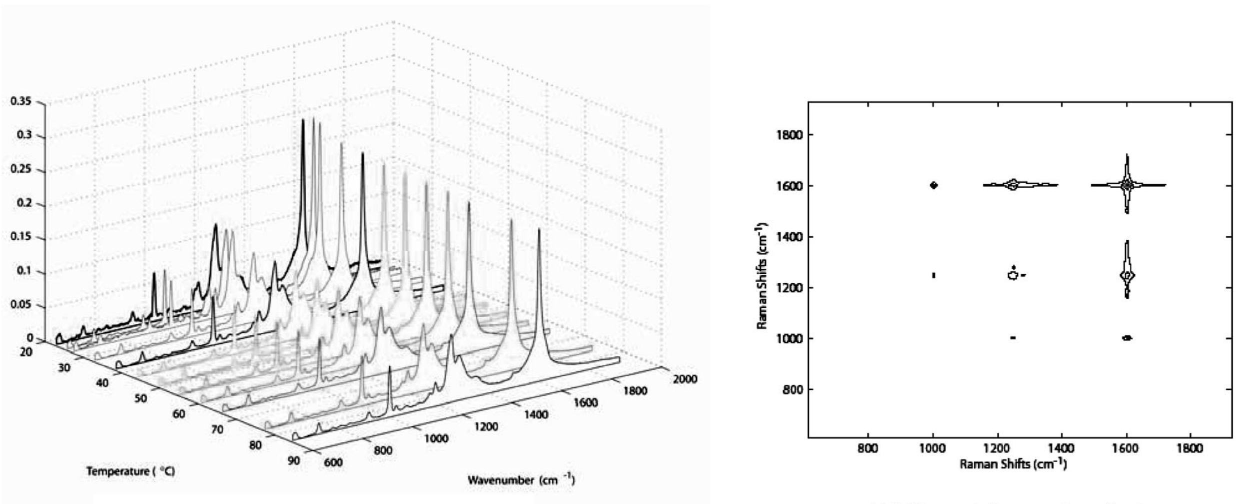
which exhibit bond lengths intermediate between typical C=C, C–C, C=O, and C–O bonds. Conversely, the C^7–O^3 bond of **1b** is closer in length to a typical C–O single bond than that of **1d**. Perhaps the most revealing feature, however, is the large difference between the O^3–H bond lengths – 0.285 Å. Unlike Madsen's assertion that the near equality of interatomic distances between O^3–H and O^4–H (1.26 Å) for **1d** shows a likely enol **A**/enol **B** equilibrium approaching unity, the much smaller O^3–H interatomic distance of 0.96 Å as compared to the O^4–H distance (1.68 Å) for **1b** supports the presence of a single enol isomer, enol **A**. Finally, it is important to note that several crystals of compound **1b** were examined; no crystal structure data consistent with either a dimeric species or enol **B** were obtained.

Based on these findings, spectroscopic studies were conducted on selected species in the solid state and/or neat liquid. The data are presented in Table 3 where δ_{H1}, δ_{H2} and δ_{H3} were determined from the neat liquid, $\nu_{\text{keto C=O}}$ was obtained in the (solid state) and $\nu_{\text{enol}\mathbf{A}\text{ C=O}}$ was acquired in the neat liquid and/or (solid state).

Table 3. Diketone equilibria in neat liquid/solid state.

	Method	$K_{K\rightarrow E\mathbf{A}}$	δ_{H2} / pm $\tilde{\nu}_{\text{keto C=O}}$ / cm^{-1}	$K_{E\rightarrow E}$ (b→a)	δ_{H1}, δ_{H3} / ppm $\tilde{\nu}_{\text{enol}\mathbf{A}\text{ C=O}}$ / cm^{-1}
1a	NMR	>> 1	not detected	>> 1	6.5, 15.2
	Raman	>> 1	not detected	>> 1	1602 (1598)
	IR	>> 1	not detected	>> 1	1603 (1599)
1b	Raman	>> 1	not detected	>> 1	1607 (1603)
	IR	>> 1	not detected	>> 1	1610
1c	Raman	>> 1	not detected	>> 1	1610 (1612)
	IR	>> 1	not detected	>> 1	(1585)
1d	Raman	>> 1	not detected	>> 1	1594 (1601)
	IR	>> 1	not detected	>> 1	(1599)
2a	NMR	<< 1	5.6	not detected	not detected
	IR	<< 1	(1685, 1710)	not detected	not detected
2b	IR	<< 1	(1688, 1708)	not detected	not detected
2c	IR	<< 1	(1696, 1715)	not detected	not detected
2d	IR	<< 1	(1687, 1700)	not detected	not detected
2e	IR	<< 1	(1690, 1702)	not detected	not detected
3b	IR	NA	(1732, 1761)	not detected	not detected

The results of this solid state-neat liquid study are informative. Given the chelated *cis*-enol **A** crystal structure for **1b**, solid state and neat liquid IR and Raman spectroscopic experiments confirm that the resonances at 1610 cm^{-1}, 1607 cm^{-1}, and 1603 cm^{-1} arise from the chelated *cis*-enol form **A**. Likewise, the neat liquid ^{1}H NMR of **1a** is indicative of the chelated *cis*-enolic structure. Vide infra, this supports the presence of a single enol form for diketones **1a**–**d**, that of enol **A**. Another trend apparent from the IR data is the observation of two C=O bands for the 2-fluoro-1-aryl β-diketones **2a**–**e**, evidence that these compounds exist solely as diketo tautomers. This is again corroborated by the neat liquid ^{1}H NMR of **2a**, which shows a resonance arising from the H^2 proton centered at



a) Solid → liquid transition spectral series for **1a**.

b) 2-D correlation spectrum for **1a**.

Figure 3. Raman spectra of **1a**.

δ = 5.6 ppm, (d, 1 H, $^{1}J_{H,F}$ = 50.1 Hz). Likewise, the solid-state IR of compound **3b**, which can only exist as the diketone, displays two C=O bands at 1732 and 1761 cm^{-1}.

A more detailed Raman spectroscopic study was undertaken on 4,4,4-trifluoro-1-phenyl-1,3-butanedione (**1a**) to ascertain whether multiple chemical species were present in the solid-state and neat liquid. The results are shown in Figure 3, where frame a depicts Raman spectra collected from **1a** as the sample underwent a solid→liquid transition from 20–84 °C and frame b shows a Hilbert–Noda synchronous two-dimensional (2-D) correlation spectrum.

The solid→liquid phase transition study of **1a** involved a series of spectra collected at each temperature. The sample temperature was held constant for a minimum of ten minutes between the incremental temperature increases. These spectra showed no change over time or the temperature range of the study. In Figure 3, frame a, the observation of a lone, well-defined enolic C=O band at 1598 cm^{-1} in the solid state (1602 cm^{-1} as a neat liquid) coupled with the absence of bands above 1650 cm^{-1} suggests the presence of enol form **A** which apparently does not undergo any appreciable tautomerization during phase transition. If **1a** were a mixture of enol tautomers in the solid state or neat liquid, one would anticipate that the C=O band would be shifted to higher wavenumber and be somewhat broader in appearance than the sharp C=O band observed.

Two-dimensional (2-D) correlation spectroscopy was used to study which vibrational features were more susceptible to change during the phase transition from solid to liquid state.[15] The 2-D spectrum of **1a** shows a strong, direct correlation between the C=O band and the C–C–O bend at 1230 cm^{-1}, while being somewhat weakly correlated to the C–F stretches at 1169, 1181 and 1353 cm^{-1} and the C–H out-of-plane bend at 990 cm^{-1}. This indicates possible torsional adjustment of the molecule during the phase transition, but the lack of complexity in the 2-D spectrum and the absence of any new vibrational features in the Raman series corroborate the presence of a single chemical species. Taken together, these facts are consistent with a chelated *cis*-enol structure (enol **A**) for β-diketone **1a**, see Table 1.

Solution State Studies: NMR/Raman Spectroscopy

To assess whether the keto–enol and enol–enol equilibria for β-diketones **1a**–**d** and **2a**–**e** were modulated in the solution state, 0.20 M solutions of compounds **1a**–**d** were prepared in sealed NMR tubes and ^{1}H NMR (CDCl$_3$ or [D$_6$]-DMSO) and Raman spectra (CDCl$_3$ or CH$_3$CN or [D$_6$]-DMSO) collected. Compounds **2a**–**e** and **3b** were examined by ^{1}H NMR in CDCl$_3$. The results are recorded in Table 4.

The data in Table 4 reflect three distinct trends. For β-diketones which are not fluorinated in the 2-position (**1a**–**d**), a preference for *cis*-enol form **A** is indicated by the predominance of a ^{1}H NMR resonance at δ(enol-H^{1}) = 6.4–6.9 ppm ([D$_6$]DMSO), and Raman bands for enol **A** at $\tilde{\nu}$(enol) = 1590–1620 cm^{-1} ([D$_6$]DMSO, CH$_3$CN). The observation that δ_{H3} (enol-H^{3}) moves to a lower chemical shift in [D$_6$]DMSO relative to that of CDCl$_3$ suggests that polar, aprotic solvents may disrupt the intramolecular H-bonding of the chelated *cis*-enol form, see Figure 4.

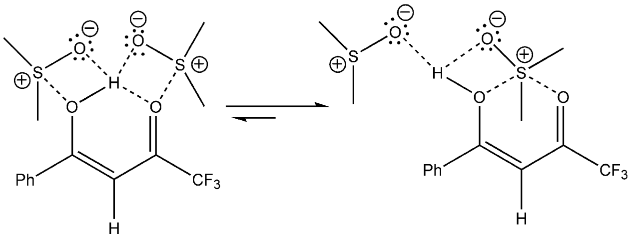


Figure 4. Disuption of *cis*-enol chelation.

Furthermore, and in accord with previous results,[1] the 1-aryl-2-fluoro β-diketones **2a**–**e** demonstrate only the diketo form, as evidenced by ^{1}H NMR resonances: δ(H^{2}) =

Table 4. Solution state diketone equilibria constants.

	Method	$K_{K\rightarrow E(A)}$		$K_{E\rightarrow E}$		% Hydrate
	NMR Raman		δ / ppm [ ]: δ_{H1} in [D$_6$]DMSO ( ): δ_{H2} in [D$_6$]DMSO { }: δ_{H2} in CDCl$_3$ $\tilde{\nu}$ / cm^{-1} [ ]: in [D$_6$]DMSO	(b→a)	δ / ppm [ ]: δ_{H3} in [D$_6$]DMSO { }: δ_{H3} in CDCl$_3$ $\tilde{\nu}$ / cm^{-1} [ ]: in [D$_6$]DMSO ( ): in CH$_3$CN	[D$_6$]DMSO (600 h)
1a	NMR	39.0	[6.8], (4.8)	>> 1	[14.2], {15.2}	41
	Raman	>> 1	not detected	>> 1	[1594], (1599)	
1b	NMR	>> 1	[6.9]	>> 1	[10.8], {11.0}	50
	Raman	>> 1	not detected	>> 1	(1608)	
1c	NMR	>> 1	[6.4]	>> 1	[14.1], {14.7}	46
	Raman	>> 1	not detected	>> 1	(1613)	
1d	NMR	2.2	[6.6], (4.2)	>> 1	[16.3], (16.1)	29
	Raman	> 1	[1703]	>> 1	[1603], (1620)	
2a	NMR	<< 1	(5.6), {5.7}	not detected	not detected	45
2b	NMR	<< 1	(5.5), {5.6}	not detected	not detected	60
2c	NMR	<< 1	(5.5), {5.6}	not detected	not detected	52
2d	NMR	<< 1	(5.4), {5.5}	not detected	not detected	35
2e	NMR	<< 1	(5.6), {5.7}	not detected	not detected	41
3b	NMR	<< 1	not detected	not detected	not detected	70

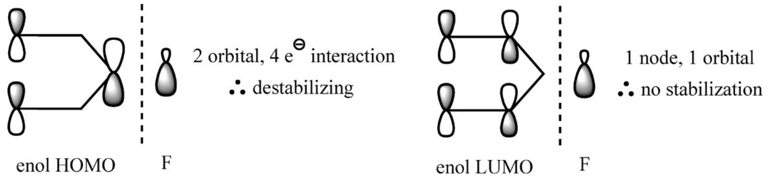


Figure 5. Enol-F FMO interaction.

Table 5. 1,3-Diketone solution component mixtures for **1a** and **1d**.

	Method	Component % of solution diketo		enol **A**		enol hydrate	
1a	NMR (δ / ppm)	H^1: 4.8		H^2: 6.8, H^3: 14.2		H^4: 6.8, H^5: 7.1, H^6: 3.4 (var)	
	Raman ($\tilde{\nu}$ / cm^{-1})	not observed		1594		> 3000	
Time / h	Conc. / mol/L	0.20	0.0016	0.20	0.0016	0.20	0.0016
0		2.4	2.3	94.0	94.2	3.6	3.5
600		0.0	0.0	59.0	58.0	41.0	42.0
1750		0.0	0.0	0.0	0.0	100	100
1d	NMR (δ / ppm)	H^1: 4.2		H^2: 6.6, H^3: 16.3		H^4, H^5: not observed H^6: 3.3	
	Raman ($\tilde{\nu}$ / cm^{-1})	1703		1603		> 3000	
Time / h	Conc. / mol/L	0.20	0.0016	0.20	0.0016	0.20	0.0016
0		21.0	21.2	75.9	75.8	3.1	3.0
600		23.2	23.3	47.8	48.1	29.0	28.6
1750		23.0	23.0	47.9	48.3	29.1	28.7

5.4–5.7 ppm in both the weakly polar $CDCl_3$ and strongly polar [D_6]DMSO. We rationalize this on the basis of frontier molecular orbital theory as depicted in Figure 5.

The net destabilizing effect displayed in Figure 5 arises from the two-orbital, four-electron interaction of the enol HOMO (pentadienyl equivalent) and the filled fluorine sp^3 hybrid orbital. In addition, the enol LUMO has a node at the carbon center adjacent to the fluorine, which provides no stabilization for the enol form.

Finally, formation of hydration products caused by the slow encroachment of water into the solution was noted. As the data from Table 4 show, the extent of hydration for trifluoromethyl 1,3-diketones **1a**–**c** and **2a**–**c** was generally found to be higher than that of the non-trifluoromethylated 1,3-diketones. A more detailed study of the trifluoromethyl 1,3-diketone rate of hydration is ongoing and will be addressed separately.

To investigate the influence of diketone concentration on the solution state equilibria, solutions of compounds **1a** and **1d** (0.0016–0.20 M in [D_6]DMSO) were analyzed by ^1H NMR and Raman spectroscopy at specified time intervals over a 1750 h period. Table 5 shows representative results of this study at two different concentrations, 0.20 M and 0.0016 M. Raman spectra were collected to qualitatively confirm the presence of tautomeric forms and the formation of hydrated species. Solution mixture component ratios were determined by noting ^1H NMR chemical shifts for the species of interest, $\delta(H^1–H^6)$, and integrating the signals to obtain relative amounts of each component for each concentration.

Based on the results in Table 5, varying the concentration over three orders of magnitude shows no appreciable effect on the keto→enol equilibrium for either β-diketone. For **1a**, the measured keto→enol equilibrium constant ($K_{\text{keto}\rightleftharpoons\text{enol}}$) ≈ 39 is transitory in nature due to the continued growth of the enol hydrate species. For **1d**, however, the determination of $K_{\text{keto}\rightleftharpoons\text{enol}} \approx 2.2$ is likely a true constant given the absence of change in the component ratios over the final 1150 hours of the investigation.

Conclusions

Our efforts reveal new facts concerning the keto–enol and enol–enol behavior exhibited by electron deficient aromatic β-diketones in the solid state, as neat liquids and in polar, aprotic solvents. In contrast to previous work,[10,11] our X-ray crystallographic results as well as solid state and neat liquid spectroscopic measurements support the presence of a single chelated *cis*-enol isomer that is conjugated with the aryl ring for the β-diketones in this study which are not fluorinated in the 2-position. Whereas solid state, neat liquid and solvent studies reveal that 2-fluoro-1-aryl β-diketones exist in the diketonic form. In the polar, aprotic solvent [D_6]DMSO, trifluoromethylated aryl β-diketones equilibrate from the *cis*-chelated enol **A** form and a small proportion of the diketone to a hydrated species, while 2-fluoro-1-aryl β-diketones exhibit the diketonic form but likewise undergo complete hydration if the solutions are allowed to stand. Non-fluorinated β-diketones equilibrate rapidly from the chelated *cis*-enol **A** form to a larger proportion of the diketo form and, in general, form enol hydrates in much lower proportion than fluorinated β-diketones.

Experimental Section

CCDC-797427 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental and instrumentation parameters.

Acknowledgments

The authors would like to thank the Georgia Gwinnett College (GGC) and USMA Faculty Research Funds for providing financial support for this work, USMA Photonics Research Center for Raman support and the NCSU X-ray facility for crystallographic support. The views expressed in this academic research paper are those of the authors and do not necessarily reflect the official policy or position of the U. S. Government, the Department of Defense, or any of its agencies.

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Received: October 25, 2010