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Tautomeric Equilibria of 3-Formylacetylacetone: Low-Temperature NMR Spectroscopy and ab Initio Calculations

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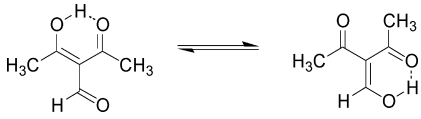

Keto−enol tautomerization of 3-formylacetylacetone has been studied by NMR spectroscopy, ab initio, and DFT calculations in the gas phase and continuum solvation. By employing very low temperatures in a freonic solvent, tautomeric and conformational equilibria in the slow exchange regime were analyzed in detail. The β-tricarbonyl compound always adopts a structure with an enolized keto group irrespective of an increasing dielectric constant of the solvent when lowering the temperature of the Freon mixture. This experimentally observed tautomeric distribution of 3-formylacetylacetone is correctly reproduced by continuum solvated DFT calculations.

Because of their importance as active methylene synthons in organic synthesis as well as their occurrence as structural elements in natural products, the structure of β-tricarbonyl derivatives associated with their keto−enol tautomeric equilibria is of major interest not only to physical chemists but also to organic and biochemists. As an example, tricarbonylmethane structural units are found in various antibiotics like tetracyclines playing an important role in their antibacterial activity and their binding of metal ions.[1] On the other hand, the simple β-tricarbonyl compound 3-formylacetylacetone represents a useful synthetic building block, e.g., as a 1,3-dielectrophile in [3+3] cyclizations.[2] It can be regarded as an unsymmetrical analogue of triacetylmethane and may exist in a tricarbonyl and several monoenol tautomeric forms as indicated in Figure 1.

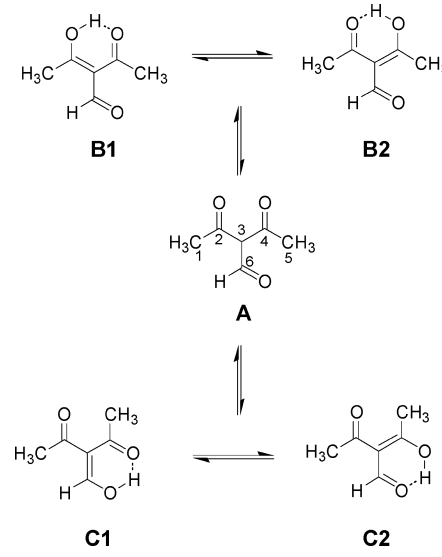

FIGURE 1. Tautomeric structures of 3-formylacetylacetone with the backbone numbering scheme indicated for **A**.

Keto−enol equilibria of a large number of carbonyl compounds have been extensively investigated in the past both experimentally and theoretically. In many cases, a strong dependence of the tautomerism on the solvent polarity as exemplified by acetylacetone has been found.[3] Surprisingly, given its role as a parent tricarbonylmethane compound there are only a few experimental and theoretical studies dealing with structural aspects of 3-formylacetylacetone.[4] In particular, a rigorous evaluation of formed tautomers and the dependence of its keto−enol equilibria on the solvent polarity, prerequisite for a better understanding of its chemical reactivity in various environments but also of potential significance when evaluating biological interactions including formation of intra- and intermolecular hydrogen bonds, has not been examined so far.

Because keto and enol tautomeric forms of carbonyl compounds have been shown to slowly exchange on the NMR time scale, NMR spectroscopic techniques have frequently been employed in their characterization at ambient temperatures.

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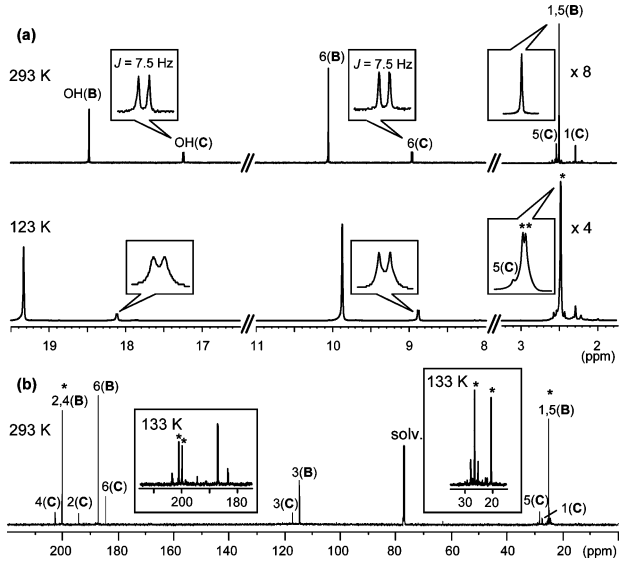

FIGURE 2. Temperature-dependent ^{1}H NMR (a) and ^{13}C NMR spectra (b) of 3-formylacetylacetone with signal assignments given for 293 K; the insets show expanded spectral regions (a) and spectral regions at 133 K (b) with signals marked by asterisks split at low temperatures.

Employing liquified freonic gases (CDF_3/CDF_2Cl) as solvent allows NMR measurements to be performed at very low temperatures below 133 K.[5] At such temperatures, many dynamical processes like hydrogen bond exchange are sufficiently slowed down to enable a more detailed characterization of molecular and complex geometries. In addition, the dielectric constant of the freonic mixture exhibits a strong dependence on temperature and effectively mimics very different solvent polarities over the temperature range accessible.[6] Thus, for a 1:1 mixture of CHF_3 and CHF_2Cl, the dielectric constant rises from 14 at 190 K to 34 at 120 K.

Temperature-dependent ^{1}H and ^{13}C NMR spectra of 3-formylacetylacetone are shown in Figure 2. Signals at 293 K are assigned based on intensities and chemical shifts as well as on additional ^{1}H−^{13}C correlation experiments. They clearly show a coexistence of tautomeric forms **B** and **C** with relative populations of about 4:1 and the absence of noticeable amounts of the tricarbonyl tautomer **A**. A stronger hydrogen bond in **B** compared to **C** is indicated by its highly deshielded OH proton. Note that with decreasing temperature further deshielding of this proton is observed and a chemical shift of 19.3 ppm at 123 K indicates its participation in a very strong intramolecular hydrogen bond.

Upon lowering the temperature, the **B**:**C** molar ratio is found to increase from 4:1 at ambient temperatures to about 6:1 at 123 K. In contrast to the well-known and significant dependence on the solvent dielectric constant of the keto−enol equilibrium in acetylacetone,[3] this moderate temperature-dependent shift in the tautomer equilibrium does not support a major contribution from polar effects of the solvent on the tautomer populations.

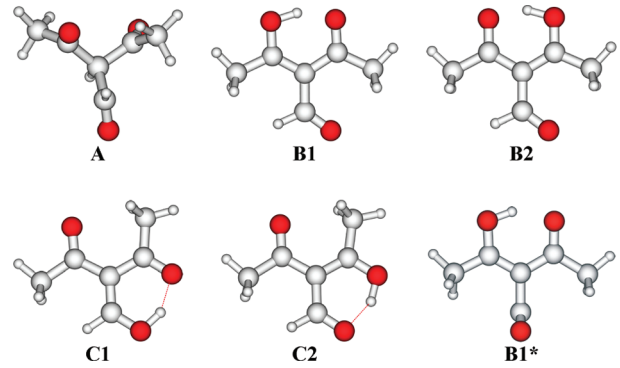

FIGURE 3. BP86/TZVPP optimized tautomeric structures of 3-formylacetylacetone in the gas phase.

Interestingly, ^{1}H and ^{13}C resonances of the pairs of equivalent CH_3 and CO groups in tautomer **B** split into two signals of equal intensity below 153 and 173 K, respectively (Figure 2). With a fast exchange between tautomers **B1** and **B2**, this observation is only compatible with a frozen rotation about the C3−C6 bond breaking the molecular symmetry of **B**. An estimate based on coalescence temperatures and chemical shift differences yields a free energy of activation for this bond rotation of about 32 kJ mol^{-1}, slightly higher compared to the energy barrier of about 20 kJ mol^{-1} around the C2−C3 bond rotation in butadiene and in line with a partial C3−C6 double bond character. On the basis of an observed scalar coupling of ^{3}J(H6,OH) = 7.5 Hz, the **C1** tautomer with enolization of the formyl group and being in fast exchange with **C2** even at low temperatures is expected to be highly populated.

To gain more insight into the relative stabilities of the individual tautomers, we have performed additional ab initio and DFT calculations on the keto−enol equilibrium of 3-formylacetylacetone in the gas phase and continuum solvation. As in related studies,[7] we initially applied DFT approaches which are known for their favorable cost-benefit ratio.[8] However, because in some cases reliable predictions deserve higher level approaches,[9] we also applied perturbational approaches and coupled cluster methods. The optimized minimum structures of the keto and enol tautomers are shown in Figure 3 with their calculated relative electronic energies in the gas phase and solvent summarized in Table 1. Irrespective of the level of theory and solvent effects, tautomers **B** are found to always represent the energetically most favored structures being >30 kJ mol^{-1} lower in energy compared to the least favorable keto tautomer **A**. As previously described for acetylacetone[7c] the computed energy difference between the keto tautomer **A** and the enol tautomers **B** and **C** strongly depends on the approximation. For the present problem, however, the keto tautomer **A** is so high in energy that it is nonobservable under the experimental conditions. The energy gaps between the tautomeric forms **B** and **C** are considerably smaller. Note, however, that energy

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TABLE 1. Relative Energies (in kJ mol^{-1}) of Optimized Structures of 3-Formylacetylacetone Tautomers Calculated in the Gas Phase or Solvent (COSMO calculations)[b]

level of theory (TZVPP basis)	A	B1	B2	C1	C2
BP86	+63.4	−1.1	0.0	+5.5	+5.1
B3LYP	+49.2	+1.0	0.0	+5.3	+4.1
BHLYP	+44.8	+1.2	0.0	+4.3	+3.9
RI-MP2	+42.7	+0.1	0.0	+4.1	+4.3
SCS-MP2[a]	+30.0	−0.4	0.0	+2.5	+4.1
CCSD(T)[a]	+39.4	+0.1	0.0	+3.0	+4.0
BP86 ($\varepsilon = 3$)	+58.3	−0.5	0.0	+6.9	+6.2
BP86 ($\varepsilon = 40$)	+54.3	−0.1	0.0	+7.7	+6.6
BHLYP ($\varepsilon = 3$)	+40.4	+0.8	0.0	+4.0	+4.0
BHLYP ($\varepsilon = 40$)	+37.1	+0.5	0.0	+4.2	+4.7

[a] Single-point calculations with the RI-MP2/TZVPP optimized geometries and zero-point energies. [b] Values include zero-point energies.

TABLE 2. Dipole Moments (in Debye) of 3-Formylacetylacetone Tautomers Calculated in the Gas Phase or Solvent (COSMO Calculations)

	A	B1	B2	C1	C2
MP2	1.33	2.18	1.17	1.80	0.93
BHLYP	1.35	2.65	1.07	2.19	0.87
BHLYP ($\varepsilon = 3$)	1.60	3.25	1.28	2.73	1.02
BHLYP ($\varepsilon = 40$)	1.96	3.84	1.47	3.28	1.18

differences between **B1** and **B2** are of the same magnitude as the available accuracy of the applied methods. Likewise, energy differences between tautomers **C1** and **C2** are marginal based on the accuracy of the calculations.

The NMR experimental analysis at 293 K in Freon gave a population distribution for **B**:**C** of 4:1, which corresponds to a free energy difference of 3.3 kJ mol^{-1}. By lowering the temperature to 123 K the ratio slightly increased to 6:1, which in turn corresponds to a smaller energy difference of 1.8 kJ mol^{-1}. Note again that **B1** and **B2** as well as **C1** and **C2** are fast exchanging on the NMR time scale and cannot be distinguished experimentally. Nevertheless, calculations with BHLYP predict energy differences between **B** and **C** tautomers in solution of about 4 kJ mol^{-1} in favor of **B** in very good agreement with the experiment given the accuracy of the method.

Overall, solvent polarity does not significantly influence the relative stabilities of the various tautomers in line with the small temperature dependence of the experimental data. This can also be rationalized by the calculated dipole moments (see Table 2) which exhibit only moderate shifts when going from the gas phase to solution. The largest changes are observed for the **B1** and **C1** structures. However, given about equal contributions from **B1/B2** and **C1/C2** to the averaged structure, dipole moments and changes in dipole moments with the solvent dielectric constant are very similar for the **B** and **C** enolic forms.

Also shown in Figure 3 is the transition structure **B1*** optimized for a C3−C6 bond rotation in **B1**. RI-MP2 energy calculations on **B1*** reveal a rotation barrier in the gas phase of about 33 kJ mol^{-1} in very good agreement with the free energy of activation as estimated from the experimental data (vide supra).

Enolizable β-triketones are known to be effectively aminated by the use of hexamethyldisilazane.[10] By reaction of the latter with 3-formylacetylacetone, regioselective amination at its aldehyde group gives the 3-aza analogue in 74% yield. Likewise, the reaction of 3-formylacetylacetone with chlorotrimethylsilane proceeded with similar regioselectivity to give 3-(trimethylsilyloxymethylene)pentane-2,4-dione (Figure 4).[2c] Regioselectivity may be attributed to the enol OH in tautomers **B** involved in a very strong intramolecular hydrogen bond (vide supra). Inspection of the crystal structure of the amination product revealed an enaminodiketone tautomeric structure with an intramolecular N−H···O hydrogen bond as shown in Figure 4.[11] The 3-(aminomethylene)pentane-2,4-dione enamine tautomer is also found to form exclusively even under varying solvent conditions[12] and our calculations clearly confirm its significantly lower energy compared to that of iminoenol and iminodiketone tautomers (see the Supporting Information).

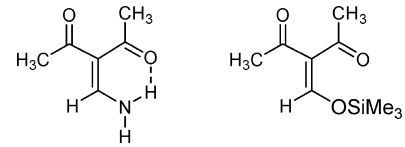

FIGURE 4. 3-(Aminomethylene)pentane-2,4-dione (left) and 3-(trimethylsilyloxymethylene)pentane-2,4-dione (right).

In summary, our experimental results indicate a preference of 3-formylacetylacetone to adopt tautomeric structures **B** and this preference applies for solvents of both low and high dielectric constants. Calculated relative energies also predict the absence of noticeable amounts of the keto tautomer **A** due to its unfavorable electronic energy. The very good agreement between calculations and the experiment may be attributed to the steric and electronic similarity of the experimentally observed enolic structures (planarity). It thus can be expected that the thermodynamic corrections and consequently the errors in the calculated relative energies stemming from inherent deficiencies of the continuum models are similar for all enol forms.

Experimental Section

3-Formylacetylacetone was prepared according to the literature by reaction of acetylacetone with triethyl orthoformate and acetic anhydride.[2a]

The deuterated freon mixture $CDClF_2/CDF_3$ was prepared as described[13] and handled on a vacuum line that was also used for the sample preparation. NMR experiments were performed at a proton resonance frequency of 500 MHz. Temperatures were adjusted by a Eurotherm Variable Temperature Unit to an accuracy of ±1.0 °C. ^{1}H chemical shifts in a freon mixture were referenced relative to $CHClF_2$ ($\delta_H = 7.13$ ppm).

For the keto form of 3-formylacetylacetone force field based conformational searches have been performed (MMFF94 force field, mixed MCMM/LM search algorithm, 5000 steps) employing the Macromodel V8.0 suite by Schrodinger Inc. The generated conformers were subsequently optimized on the DFT level (RI-BP86/SVP) and the lowest conformer has been used for higher level calculations.

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All structure optimizations have been performed with the Turbomole V5.8 program package and were done on RI-BP86, B3LYP, BHLYP, and RI-MP2 levels of theory employing a TZVPP basis set. In the present paper the electrostatic contributions of the solvent were estimated by using the COSMO approach as implemented in TURBOMOLE with dielectric constants of $\varepsilon = 3$ and 40 in order to simulate solvents of varying polarity. The nonelectrostatic terms of the COSMO approach have been determined by BP86/6-31++G(d,p) single point calculations employing the Gaussian03 program package on the BP86/TZVPP optimized geometries in the respective dielectric. The CCSD(T)/TZVPP and (SCS)-MP2/TZVPP single-point calculations were performed with MOLPRO on RI-MP2/TZVPP optimized geometries.

The transition state for C3−C6 bond rotation has been calculated with STATPT starting from a reasonable initial guess and following the gradient of negative eigenvalue of the formyl group rotation. The TS has been checked again by calculating the Hessian analytically (AOFORCE) on a BHLYP/TZVPP level of theory.

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Supporting Information Available: Procedures for syntheses; experimental and calculated ^{1}H chemical shifts, absolute energies, zero-point energies, and number of imaginary frequencies of 3-formylacetylacetone tautomers; ^{13}C and ^{1}H NMR spectra of 3-(aminomethylene)pentane-2,4-dione; and relative and absolute energies, zero-point energies and number of imaginary frequencies of optimized structures of 3-(aminomethylene)pentane-2,4-dione tautomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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