Determination of Solvent Effects on Keto–Enol Equilibria of 1,3-Dicarbonyl Compounds Using NMR

W

Revisiting a Classic Physical Chemistry Experiment

Gilbert Cook* and Paul M. Feltman

Department of Chemistry, Valparaiso University, Valparaiso, IN 46383; **Gil.Cook@valpo.edu*

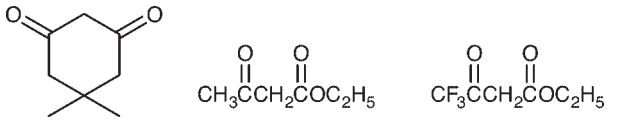
"The influence of solvents on chemical equilibria was discovered in 1896, simultaneously with the discovery of keto–enol tautomerism in 1,3-dicarbonyl compounds" *(1)*. The solvents were divided into two groups according to their ability to isomerize compounds. The study of the keto–enol tautomerism of β-diketones and β-ketoesters in a variety of solvents using proton NMR has been utilized as a physical chemistry experiment for many years *(2, 3)*. The first reported use of NMR keto–enol equilibria determination was by Reeves *(4)*. This technique has been described in detail in an experiment by Garland, Nibler, and Shoemaker *(2)*.

The most commonly used β-diketone for these experiments is acetylacetone (Scheme I). Use of proton NMR is a viable method for measuring this equilibrium because the tautomeric keto–enol equilibrium is slow on the NMR time scale, but enol (**2a**)–enol (**2b**) tautomerism is fast on this scale *(5)*.

It has been observed that acyclic β-diketones and β-ketoesters follow Meyer's rule of a shift in the tautomeric equilibrium toward the keto tautomer with increasing solvent polarity *(6)*. The implicit or explicitly stated rationale for this observation in molecules such as acetylacetone is that the keto form is more polar than the enol form and hence is more stable in polar solvents *(2, 3, 7–10)*. However, the concept that the keto form is more polar than the enol form is questionable *(11)*. Theoretical calculations *(12)* and actual experimental measurements *(13)* show that the keto tautomer of acetylacetone has a lower dipole moment than the enol tautomer in both the gas phase and solution.

Pedagogical Benefits for Students

The classic experiment that uses proton NMR to determine the equilibrium of 1,3-dicarbonyl compounds is expanded (i) to give an in-depth analysis of factors influencing solvent effects in tautomeric equilibria and (ii) to illustrate the use of molecular modeling in determining the origin of a molecule's polarity. The experiment's original benefits of using proton NMR as a noninvasive method of evaluating equilibrium are maintained.

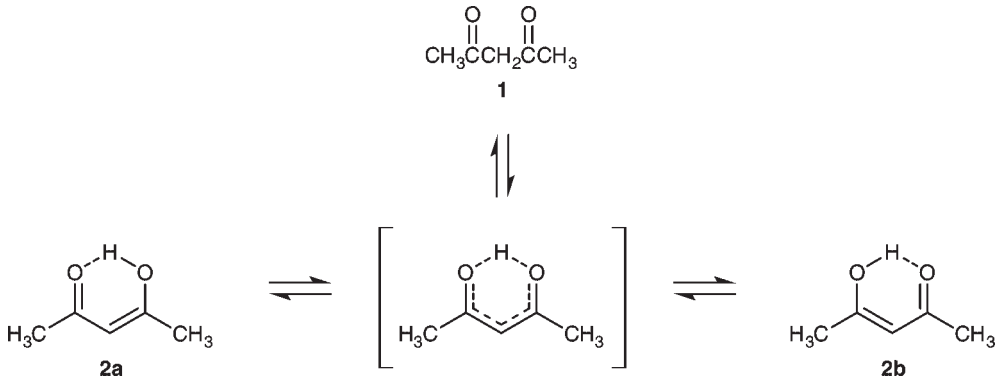


3 **4** **5**

Figure 1. The β-dicarbonyl compounds studied in the experiment.

Experimental Procedure

Observations of the solvent effects for three other 1,3-dicarbonyl compounds in addition to acetylacetone help to identify the sources of these solvent effects. These three compounds are dimedone, **3**, ethyl acetoacetate, **4**, and ethyl 4,4,4-trifluoroacetoacetate, **5** (Figure 1). Dilute (0.05 M) solutions are used to avoid dimer formation of the enol tautomer. The two solvents are deuterochloroform (a relatively nonpolar solvent) and dimethylsulfoxide (DMSO, a polar aprotic solvent). The percent tautomer composition for each of the compounds is determined by integrating the area under the ketone methylene proton signal and the enol vinyl proton signal. The keto methylene signal appears in the 3.4 to 3.8 ppm chemical shift region and the enol vinyl proton signal appears in the 5.1 to 5.7 ppm chemical shift region. The enol integration area must be weighted by two to ac-



1 **2a** **2b**

Scheme I. Keto–enol tautomerism of acetylacetone.

count for there being only a single enol vinyl proton as compared to two protons for the keto methylene. Molecular modeling calculations are carried out to determine the relative gas phase energies and dipole moments of these four compounds.

Hazards

Deuterochloroform and ethyl 4,4,4-trifluoroacetoacetate are skin and eye irritants, toxic by inhalation or ingestion. Dimethyl sulfoxide is harmful if swallowed, inhaled, or absorbed through the skin. Ethyl acetoacetate is flammable and harmful if swallowed or inhaled. Acetylacetone is harmful if inhaled or swallowed and is a possible teratogen

Discussion

The reasons for choosing these four compounds to study are as follows. Dimedone, **3**, is a cyclic trans-fixed β-carbonyl compound *(17)* in contrast to acetylacetone, which is acyclic and exists almost exclusively in the cis form. This means that intramolecular hydrogen bonding is impossible for dimedone whereas it is present in acetylacetone, **1**. Ethyl 4,4,4-trifluoroacetoacetate, **5**, with electronegative fluorine atoms attached to the carbon adjacent to a carbonyl is contrasted with ethyl acetoacetate, **4**, and both of these acyclic β-dicarbonyl compounds are contrasted with acyclic acetylacetone and cyclic dimedone. The percent enol tautomer present at equilibrium for these four compounds in two different solvents is shown in Table 1. The pK_a in water for each of the compounds is also listed in Table 1.

Semi-empirical AM1 calculations give reasonable values for the dipole moments, but not for the energies. For example it has been shown experimentally that the enol form of acetylacetone is favored in the gas phase *(18),* but AM1 calculations indicate the opposite. However, if ab initio density functional calculations are carried out, a value corresponding to experiment is found. Thus, even though density functional calculations are more time-consuming, the advantage of values that are in better agreement with experimentation is worth it. We use Spartan for Windows (both the 2002 and the 2006 versions) *(19)* and have found that the B3LYP/6-31* model gives results that are most consistent with experimental measurements. It is expected that other similar modeling software with DF capability will perform similarly. The student should also determine the dihedral angles between carbonyl planes in the keto tautomers to help show the source of the molecule's dipole moment. All of these data are shown in Table 2.

Table 1. Percent Tautomer Composition and pK_a

Compound	% Enol			pK_a
	$CDCl_3$	DMSO	Neat	
Acetylacetone	86	63	80	9.1 *(14)*
Dimedone	7	95	—	5.3 *(15)*
Ethyl acetoacetate	3	0	8	11.0 *(14)*
Ethyl 4,4,4,-trifluoroacetoacetate	85	99	89	7.9 *(16)*

Some of the factors that the student will consider in explaining the position of the equilibrium are the presence or absence of intramolecular hydrogen bonding in the enol tautomer; the dipole moments of each of the tautomers; solvent polarity; the enthalpy and the entropy change due to both intramolecular and intermolecular hydrogen bonding; and the nature of the substituents attached to the β-dicarbonyl compound. The percent enol present for each compound in a given solvent will be discussed by the student in light of these factors *(20).* Some general observations upon which they can base their explanations are the following:

1. Cis intramolecular hydrogen bonding favors enolization enthalpically but causes a decrease in entropy.
2. A polar solvent favors the tautomer with the highest dipole moment.
3. The lowest energy form of an acyclic keto tautomer of a β-dicarbonyl compound has carbonyls that are not parallel to each other. The keto tautomer of a cyclic β-dicarbonyl compound is forced to have more nearly parallel carbonyl groups. Parallel carbonyl groups give a larger dipole moment.

Table 2. Molecular Modeling Results

Compound	Energy		Dipole Moment (Debye)		Dicarbonyl Dihedral Angles/deg
	Keto	Enol	Keto	Enol	
Acetylacetone					
AM1 (kcal/mol)	-85.6434829	-84.9097393	1.89	3.03	138.50
Density Funct. (au)	-345.794728	-346.998921	1.55	3.57	137.78
Dimedone					
AM1 (kcal/mol)	-93.8524954	-89.1683449	3.52	3.05	0.58
Density Funct. (au)	-462.529609	-462.520454	3.72	3.37	0.00
Ethyl acetoacetate					
AM1 (kcal/mol)	-131.940482	-131.478408	4.24	4.62	104.21
Density Funct. (au)	-460.332081	-460.337656	4.62	4.37	98.39
Ethyl 4,4,4-trifluoroacetoacetate					
AM1 (kcal/mol)	-279.822601	-278.407535	2.84	2.93	71.92
Density Funct. (au)	-758.049943	-758.054993	2.52	3.53	78.23

4. DMSO is a strong polar hydrogen bond acceptor *(1)* that can stabilize the enol tautomer *(21).*
5. Electronegative β-substituents increase the degree of enolization *(22).* This parallels the observation that the more acidic the β-dicarbonyl compound, the greater the enolization *(16).*
6. Hydrogen bonding solvents will decrease in entropy when ordered by solute enol tautomers.

[W]Supplemental Material

Description of the student experiment and notes for the instructor are available in this issue of *JCE Online*.

Literature Cited

1. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry,* 2nd ed.; VCR: New York, 1988; p 2.
2. Garland, E. W.; Nibler, J. W.; Shoemaker, D. P. *Experiments in Physical Chemistry,* 7th ed. (and earlier editions); McGraw-Hill: New York, 2003; pp 453–461.
3. Drexler, E. J.; Field, K. W. *J. Chem. Educ.* **1976,** *53,* 392–393.
4. Reeves, L. W. *Can. J. Chem.* **1957,** *35,* 1351–1365.
5. Koltsov, A. I. *J. Mol. Structure* **1998,** *444,* 1–11.
6. Meyer, K. H. *Ann.* **1911,** *380,* 220–242.
7. Spyridis, G. T.; Meany, J. E. *J. Chem. Educ.* **1988,** *65,* 461–462.
8. Lockwood, K. L. *J. Chem. Educ.* **1965,** *42,* 481–482.
9. Naoum, M. M.; Botros, M. G. *Indian J. Chem.* **1986,** *25A,* 427–430.
10. Toullec, J. In *The Chemistry of Enols;* Rappoport, Z., Ed.; Wiley: New York, 1990; p 361.
11. Iglesias, E. *Current Org. Chem.* **2004,** *8,* 1–24.
12. Buemi, G.; Gandolfo, C. J. *J. Chem. Soc., Faraday Trans. 2* **1989,** *85,* 215–227.
13. Cusiter, M. A.; LeFevre, R. J. W.; Millar, D.; Pierens, R. K. *Aust. J. Chem.* **1977,** *30,* 503–509.
14. Streitwieser, A.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry,* 4th ed.; Macmillan: New York, 1992; p A8.
15. Bell, R. P.; Davis, G. G. *J. Chem. Soc.* **1965,** 353–361.
16. Shukla, J. P.; Sharma, R. S. *J. Prakt. Chem.* **1990,** *332,* 619–628.
17. Eistert, B.; Reiss, W. *Chem. Ber.* **1954,** *87,* 92–108.
18. Folkendt, M. M.; Weiss-Lopez, B. E.; Chauvel, J. P., Jr.; True, N. S. *J. Phys. Chem.* **1985,** *89,* 3347–3352.
19. Wavefunction, Inc.; Irvine, CA. *http://www.wavefun.com/* (accessed Jul 2007).
20. Spencer, J. N.; Holmboe, E. S.; Kirshenbaum, M. R.; Firth, D. W.; Pinto, P. B. *Can. J. Chem.* **1982,** *60,* 1178–1182.
21. Wiberg, K. B.; Ochterski, J.; Streitwieser, A. *J. Am. Chem. Soc.* **1996,** *118,* 8291–8299.
22. Geraldes, C. F. G. C.; Barros, M. T.; Maycock, C. D.; Silva, M. I. *J. Mol. Structure* **1990,** *238,* 335–346.