# Communications to the Editor

## Thermodynamically Favored Unconjugated Enols Containing Doubly Antiperiplanar Acetal Groups

Martin G. Ettlinger* and Kenneth J. Watson

*Department of Chemistry, University of Copenhagen*
*Universitetsparken 5, 2100 Copenhagen Ø, Denmark*

Jerzy W. Jaroszewski*

*Department of Organic Chemistry*
*Royal Danish School of Pharmacy*
*Universitetsparken 2, 2100 Copenhagen Ø, Denmark*

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Enols in which the enolic double bond is not conjugated classically with additional multiple linkages are normally considerably less stable than their keto tautomers.[1] In this communication, we call attention to unconjugated enols that are easily prepared from common chemicals and isolated as crystalline substances, can be dissolved in aqueous alkali and reprecipitated by acid-like phenols, and are capable of predominating over their tautomers at equilibrium. The first representatives of these enols were isolated 100 years ago,[2,3] but their true nature has never been recognized.

The enols arise quantitatively from the enones **1** and **2** (Chart 1) by 1,4-addition of methoxide followed by acidification. When originally obtained, they were formulated as hemiacetals, and this view has persisted without being questioned until now.[4] In fact, the substances are respectively 2,4,5-trichloro-3,3,6,6-tetramethoxy-1,4-cyclohexadien-1-ol (**3**) and 2,5-dichloro-3,3,6,6-tetramethoxy-1,4-cyclohexadiene-1,4-diol (**4**) (Chart 1), as their $^1$H and $^{13}$C NMR spectra immediately demonstrate. Enol **3** is prepared in two steps from pentachlorophenol or 3-chloroaniline,[2] enol **4** in one step from chloranil (tetrachloro-2,5-cyclohexadiene-1,4-dione).[3]

The keto tautomers of **3** and **4** could not be isolated and appeared to be present to the extent of only several percent of the mixtures when the enols were allowed to stand in polar solvents.[5] Thus **3** and **4** appeared to be *thermodynamically* stable with respect to ketonization, but observation was complicated by loss of methanol.[6] To overcome this difficulty, the 3-methoxy groups in **3** were exchanged for an ethylenedioxy group to give pure samples of enol **5** and ketone **6** (Chart 1).

**Chart 1**

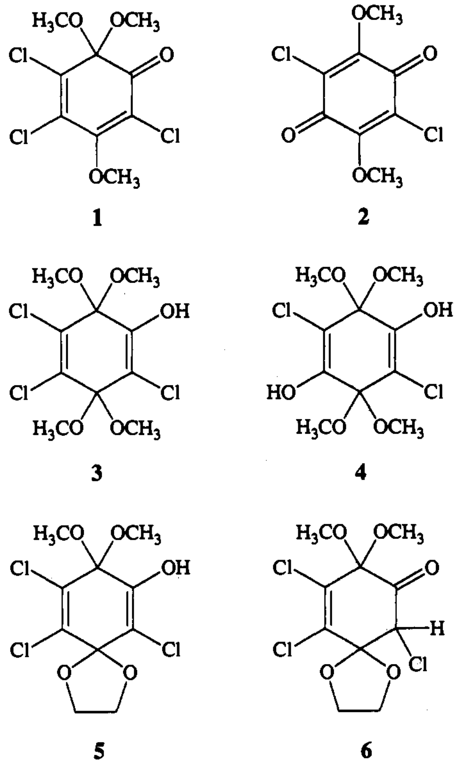

Table 1. Solvent Effects on the Keto-Enol Equilibrium between **5** and **6**[a]

| solvent | equilibrium constant [**5**]/[**6**] | chemical shift ($\delta$) of $H_\alpha$ in **6** |
|---|---|---|
| $C_6D_6$ | 0.01 | 5.07 |
| $CDCl_3$ | 0.05 | 5.30 |
| $CD_3NO_2$ | 0.07 | 5.42 |
| $CD_3CN$ | 0.10 | 5.45 |
| $(CD_3)_2CO$ | 0.25 | 5.60 |
| $CD_3CN$–$D_2O$[b] | 0.50 | c |
| $(CD_3)_2CO$–$D_2O$[b] | 0.75 | c |
| $CD_3OD$ | 0.80 | 5.54[d] |
| $CD_3CON(CD_3)_2$ | 1.00 | 5.86 |
| $(CD_3)_2SO$ | 2.30 | 6.00 |

[a] By $^1$H NMR spectroscopy at 35 °C; total concentration of **5** and **6**, 0.125 M. [b] $D_2O$ 28% by volume. [c] Exchanged for deuterium. [d] Before complete exchange.

In solution, either **5** or **6** yielded on standing the same equilibrium mixture of the two, the equilibration being greatly accelerated by traces of weak bases. The position of the equilibrium in a series of solvents is shown in Table 1. In nonpolar solvents, the keto form predominated, while hydrogen-bond-accepting solvents stabilized the enol form. For aprotic solvents, the free energy difference between **5** and **6** and the chemical shift of $H_\alpha$ in **6** were linearly correlated ($\Delta G° = 5.852 - 0.282\delta_{H_\alpha}$ kcal/mol, $r = 0.996$). The variation in chemical shift of $H_\alpha$ of **6** with solvent is that expected from C–H hydrogen bonding; thus, both **5** and **6** participate in hydrogen bonding to the solvent, though the bond to the enolic hydroxy group is stronger and varies more in energy with solvent than the bond to $H_\alpha$ of **6**. The apparent spectrophotometric p$K_a$ of the equilibrium mixture of **5** and **6** in water was 6.2, which is then an upper limit to the p$K_a$ of either component.

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[1] Hart, H. *Chem. Rev.* **1979**, *79*, 515–528. Hart, H.; Rappoport, Z.; Biali, S. E. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 1990; pp 481–589.

[2] Zincke, T.; Schaum, C. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 537–559. Zincke, T.; Broeg, W. *Liebigs Ann. Chem.* **1908**, *363*, 221–245.

[3] Jackson, C. L.; Grindley, H. S. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1631–1633. Jackson, C. L.; Grindley, H. S. *Am. Chem. J.* **1895**, *17*, 579–607, 633–658. See also: Jackson, C. L.; Torrey, H. A. *Am. Chem. J.* **1898**, *20*, 395–430.

[4] The dienone **1** was originally assigned an incorrect structure,[2] whereas **2** was well known at the time of the original work.[3] The clue to the structure of **1** appeared in 1952, when its reduction product was shown to be 2,4,5-trichloro-3,6-dimethoxyphenol: Oliverio, A.; Castelfranchi, G.; Borra, G. *Gazz. Chim. Ital.* **1952**, *82*, 115–122. Thus the probable identity of **1**, but not of **3**, was indicated in: Boit, H.-G., Ed. *Beilsteins Handbuch der organischen Chemie*, 4th ed.; Springer-Verlag: Berlin, 1970; Suppl. 3, Vol. 8, Part 3, pp 1973–1974. The incorrect hemiacetal representation[3] of **4** was accepted in the literature: Wallenfels, K.; Friedrich, K. *Chem. Ber.* **1960**, *93*, 3070–3082. Huot, R.; Brassard, P. *Can. J. Chem.* **1974**, *52*, 838–842.

[5] Aged solutions of **3** in $(CD_3)_2SO$ exhibited a weak $^1$H resonance at $\delta$ 5.61, attributable to $H_\alpha$ of the keto tautomer, and a $^{13}$C carbonyl group signal at $\delta$ 189.2; this compound accounted for 1–2% of the original amount of **3**. Similar minor signals were observed with **4**.

[6] In neutral methanol, the equilibrium ratio of **1** to **3** plus minor components was 0.45 (25 °C). The uncatalyzed loss of methoxide from the anion of **3** (p$K_a$ 5.3 in water) is slow.

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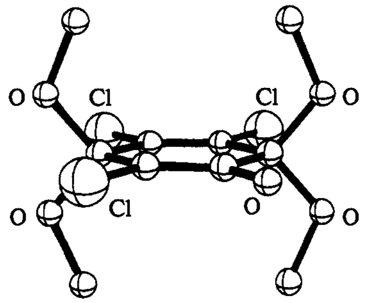

**Figure 1.** Molecular geometry of **3** as determined by X-ray diffraction (only non-hydrogen atoms are shown).

The remaining point is an explanation of the unanticipated[1,7] thermodynamic stability of these enols toward ketonization. Among the principal factors we perceive the relative conformational rigidity of the unsaturated six-membered ring, the presence of the $\alpha$-chlorine substituent,[8] and, of particular novelty, dipolar interactions between carbonyl and dimethyl acetal groups. In the solid state of both **3** (Figure 1) and **5**, the dimethyl acetal groups are found in the uncommon[9] doubly antiperiplanar (ap,ap) conformation.[10] This conformation, usually of higher energy than synclinal (sc,sc) conformations,[11] is evidently enforced by the presence of adjacent substituents on the double bonds of the ring.[9] Accordingly we expect this conformation to be maintained in the keto tautomers. Whereas an sc,sc acetal group has a negligible dipole moment, the calculated dipole moment of ap,ap conformers is about 2.5 D,[12] of the same magnitude as the dipole moment of a carbonyl group. In other words, *doubly antiperiplanar dimethyl acetal groups are inductively, though not conjugatively, the equivalent of carbonyl groups* and cause destabilization of keto tautomers by the same dipolar interactions found in 1,2- and 1,3-cyclohexanediones.[13] Indeed, under conditions where the keto tautomer of **3** is barely detectable, enol **5**, in which the dipole moment of the acetal group in the 3 position is diminished and reversed in direction, ketonizes to a much more substantial extent. In addition to whatever polar effect the chlorine atoms on the 4,5-double bond may have, they play an important steric part in maintaining the conformation of the dimethyl acetal groups and so, if indirectly, the extraordinary relative stability of the enols. The observation that 2,3,5-trichloro-6-hydroxy-2,5-cyclohexadiene-1,4-dione and chloranilic acid (2,5-dichloro-3,6-dihydroxy-2,5-cyclohexadiene-1,4-dione) retain their enolic character when their carbonyl groups are masked as acetals, though elementary and delayed by a century, is astonishing and instructive.[14]

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(7) We know only one previous example of an unconjugated, thermodynamically stable simple enol: Pratt, D. V.; Hopkins, P. B. *J. Am. Chem. Soc.* **1987**, *109*, 5553–5554. This ketone–enol pair is less acidic and equilibrates less rapidly by a large factor than **5** and **6**. See also: Capon, B.; Guo, B.-Z.; Kwok, F. C.; Siddhanta, A. K.; Zucco, C. *Acc Chem. Res.* **1988**, *21*, 135–140. Kresge, A. J. *Acc. Chem. Res.* **1990**, *23*, 43–48. Toullec, J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 1990; pp 323–398. Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 1990; pp 399–480.

(8) *Cf.*: Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 1177–1185. Capon, B.; Siddhanta, A. K.; Zucco, C. *J. Org. Chem.* **1985**, *50*, 3580–3584. Leis, J. R.; Peña, M. E.; Williams, D. L. H.; Mawson, S. D. *J. Chem. Soc., Perkin Trans. 2* **1988**, 157–162.

(9) Nørskov-Lauritsen, L.; Larsen, S.; Ettlinger, M. G.; Jaroszewski, J. W. *Acta Crystallogr.* **1982**, *B38*, 3107–3110 and references cited therein.

(10) A full account of the crystallographic work will be published elsewhere. The hydrogen atoms of the hydroxy groups of **3** and **5** are anti to C-2 and the attached chlorine and form hydrogen bonds to dimethyl acetal groups of neighboring molecules, with intermolecular OH···O contacts of 2.76–2.78 Å.

(11) Cossé-Barbi, A.; Dubois, J.-E. *J. Am. Chem. Soc.* **1987**, *109*, 1503–1511. Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019–5087.

(12) *Cf.*: Kubo, M. *Sci. Pap. Inst. Phys. Chem. Res.* (*Jpn.*) **1936**, *29*, 179–187. According to Allinger's molecular mechanics, the dipole moments of sc,sc and ap,ap dimethoxymethane are 0.25 and 2.55 D respectively.

(13) The $pK_a$ of 2,3,5-trichloro-6-hydroxy-4,4-dimethoxy-2,5-cyclohexadienone, originally considered a hemiacetal (Jackson, C. L.; MacLaurin, R. D. *Am. Chem. J.* **1907**, *38*, 127–175), is 5.15, practically the same as that of its acetal **3**.

(14) This class of enols is thus expected to be subject to broad generalization.[3,15]

(15) Torrey, H. A.; Hunter, W. H. *J. Am. Chem. Soc.* **1912**, *34*, 702–716. Jackson, C. L.; Bolton, E. K. *J. Am. Chem. Soc.* **1914**, *36*, 551–568. Jackson, C. L.; Bolton, E. K. *J. Am. Chem. Soc.* **1914**, *36*, 1473–1484.