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Explanation of Substituent Effects on the Enolization of β-Diketones and β-Ketoesters

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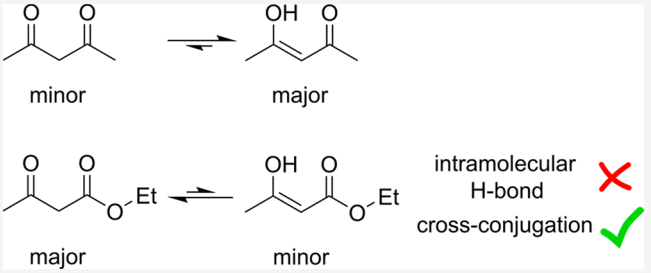
ABSTRACT: This article highlights some of the challenges in explaining simple substituent effects on keto−enol equilibria, particularly to an undergraduate audience. Quantum-chemical calculations were performed to identify the role of intramolecular hydrogen bonding, inductive effects due to electron-withdrawing groups, and cross-conjugation on the enolization of β-diketones and β-ketoesters. These insights could be applied by an instructor in order to enrich undergraduate chemistry students' understanding of this fundamental reaction.



KEYWORDS: *Upper-Division Undergraduate, Graduate Education/Research, Physical Chemistry, Organic Chemistry, NMR Spectroscopy, Computational Chemistry*

INTRODUCTION AND BACKGROUND

The study of keto−enol tautomerization is a popular undergraduate physical chemistry experiment. Typically, these experiments entail the use of ^{1}H NMR spectroscopy to measure the equilibrium constants of various tautomerization processes. For example, Drexler and Field were among the first to report such an experiment on the study of solvent and temperature effects on the keto−enol equilibria of β-diketones and β-ketoesters.[1] Since then, many variants of this experiment have been developed including the study of electronic and substituents effects,[2,3] solvation thermodynamics,[4−6] molecular conformation,[7] as well as the kinetics and mechanism[8] of this fundamental organic reaction.

Despite the popularity of this classic experiment, it is to the authors' surprise that there is currently not a clear explanation for simple substituent effects such as the preferential enolization of β-diketones (e.g., **1**) relative to corresponding β-ketoesters (e.g., **2**), or the enol-promoting effect of electron-withdrawing groups (e.g., **3**). Figure 1 presents the experimentally measured enol content of four representative molecules: acetylacetone (**1**), ethyl acetoacetate (**2**), 1,1,1-trifluoropentane-2,4-dione (**3**), and ethyl-4,4,4-trifluoroacetoacetate (**4**).

While it is known experimentally that the equilibrium position depends strongly on solvent polarity,[9] the data in Figure 1 are all measured in chloroform (a relatively nonpolar solvent) so that one can directly assess substituent effects. Comparison between compounds **1** and **2** clearly indicates that, in contrast to β-diketones, the keto form of β-ketoesters is the thermodynamically preferred tautomer.[10] In a Communication published in this *Journal*,[2] the stabilization of the keto tautomer of methyl acetoacetate has been attributed to the *net* effect of electron donation via a lone-pair resonance in the ester. As we will see later, this statement is indeed correct; however, it also raises a number of important questions. In particular, the effect of the lone-pair resonance would also be present in the enol, so it is unclear why the effect would be stronger in the β-dicarbonyl. Figure 2 depicts the key resonance structures of the keto and enol forms of ethyl acetoacetate (**2**). From freshman chemistry one might naively suggest that there is a greater resonance stabilization of the enol, since the formal negative charge on the carbonyl oxygen (resonance contributors I and II; Figure 2) should strengthen the intramolecular hydrogen bond. As such, it seems counterintuitive that electron-donating substituents (resonance donation) should disfavor the enol.

Comparison of acetylacetone (**1**) and 1,1,1-trifluoropentane-2,4-dione (**3**) as well as ethyl acetoacetate (**2**) and ethyl trifluoroacetoacetate (**4**) reveals another interesting substituent effect, where the electron-withdrawing substituents (inductive withdrawal) favor the enol form. Notably, the trifluoromethyl group counteracts the effect of the electron-donating ester group such that the enol form of **4** is the major tautomer (Figure 1). A common explanation of the enol-promoting effect of electron-withdrawing groups is that there is a direct correlation between the carbon (C−H) acidity of the β-dicarbonyl compound and the stability of the enol.[5] However, this is an empirical observation rather than an actual explanation of the substituent effect. Furthermore, it is conceptually misleading to rationalize

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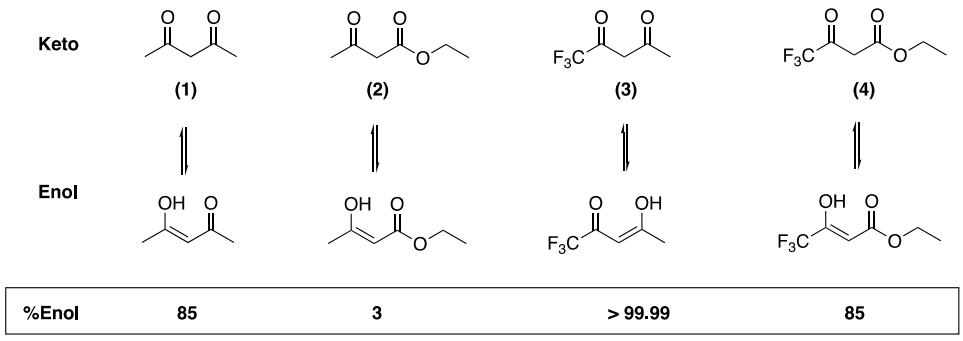

Figure 1. Percent of the enol form present in chloroform solution at 298 K. Data obtained from refs 2 and 5.

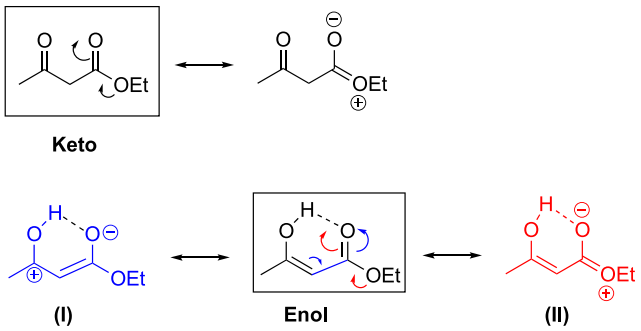

Figure 2. Resonance structures of the keto and enol tautomers of ethyl acetoacetate (**2**).

the degree of enolization on just the acidity of the keto isomer. This is because the keto−enol equilibrium constant (K_E) depends on not only the carbon acidity of the β-dicarbonyl but also the oxygen (−OH) acidity of the corresponding enol. As shown in Figure 3, deprotonation of the carbon acid and

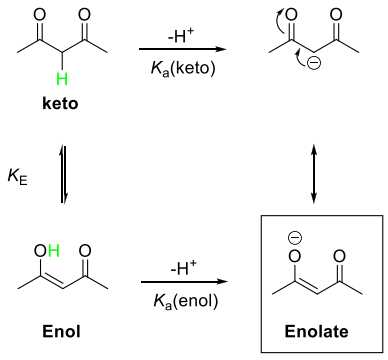

Figure 3. Enolate (boxed) is the conjugate base of the keto (C−H) and enol (O−H) acids. The acidic protons are shown in green.

deprotonation of the oxygen acid give the same species; the conjugate base of the keto and enol forms is the enolate (Figure 3; boxed). The acidic protons are shown in green and do not imply an intramolecular conversion of the keto and enol tautomers.

Accordingly, the keto−enol equilibrium constant (K_E) is directly related to the relative acidities of the two tautomers.

$$pK_E = pK_a(\text{keto}) - pK_a(\text{enol}) \quad (1)$$

In other words, the more acidic tautomer (with lower pK_a value) is also the thermodynamically less stable tautomer. Framed in this manner, the enol-promoting effect of electron-withdrawing groups is a result of a *preferential* enhancement of the C−H acidity of the keto relative to the O−H acidity of its enol. To better illustrate this point, we searched the literature for systems with reported experimental pK_a and pK_E values; limited data are available. Figure 4 shows the pK_a data for the keto and

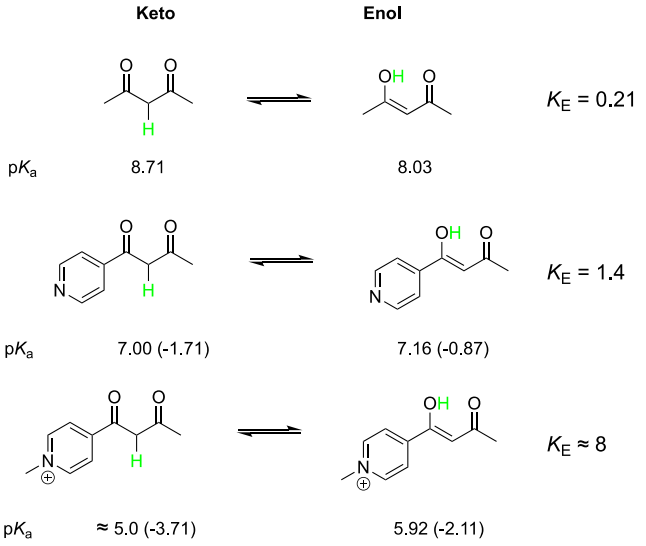

Figure 4. Experimental aqueous pK_a values and tautomerization constants (K_E) of some asymmetrical β-diketones and their enols.[11] The values in parentheses refer to the change in pK_a value relative to acetylacetone and its enol. Acidic protons are shown in green.

enol forms of a series of unsymmetrical β-diketones measured using stopped-flow spectrophotometry in water (values in nonaqueous solvents are unavailable, but this does not affect the argument presented in any way). As shown, the introduction of an electron-withdrawing substituent, pyridyl and *N*-methylpyridinium, increases *both* the C−H and O−H acidity of the two tautomers, and that effect is generally more pronounced in the β-diketone (change in pK_a shown in parentheses), giving rise to an increase in enolization—see eq 1. The molecular origin of the enol-promoting effect is presumably due to the strengthening of the intramolecular hydrogen bond associated with increased O−H acidity and/or inductive destabilization of the keto form. However, to the best of our knowledge, there has been no systematic examination of these explanations. The goal of this article is to use quantum-chemical calculations to develop an explanation of these substituent effects that will enhance undergraduate chemistry students' (and our!) understanding of this fundamental organic reaction.

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COMPUTATIONAL DETAILS

All electronic structure calculations were performed using the Gaussian16[12] program. Geometry optimizations were performed at the M06−2X/6-31G(d) and B3LYP-D3(BJ)/6-31G(d) levels of theory, and frequency calculations were performed at the same level to ascertain that these are true minimum-energy structures. Systematic conformer searches were also performed to determine the lowest-energy conformer for each species. The natural bond orbital (NBO) analysis[13] and Wiberg bond-order calculations[14] were performed using Gaussian16. The Supporting Information contains detailed instructions on how to perform an NBO calculation using the Gaussian program.

RESULTS AND DISCUSSION

Before we proceed further, the astute reader may have already noticed that the enols presented in Figure 1 are only one of the possible enolic isomers. For example, there are three possible isomers for the enol form of **2** (Figure 5). The structures

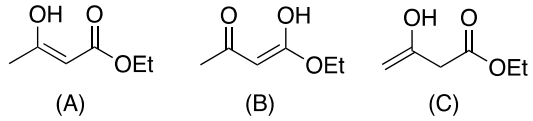

Figure 5. Isomers of the enol form of ethyl acetoacetate **2**.

presented in Figure 1 correspond to the most stable isomer of each enol in the gas phase, which is typically isomer A or B. For compound **3**, isomer B is slightly lower in energy than isomer A by ∼0.7 kcal mol^{-1}. In all cases, isomer C is the least stable, and this can be understood in terms of the degree of substitution of the alkene moiety—more-substituted alkenes are more stable than less-substituted ones due to hyperconjugation (Zaitsev's rule).[15] The relative energies of the isomers A to C of the enols of compounds **1**−**4** are available in Table S1 in the Supporting Information.

Intramolecular hydrogen bonding and inductive destabilization of the keto are potential factors that could explain some of the substituent effects on keto−enol equilibria. However, cross-conjugation[16] is another effect that is rarely mentioned in this context. In a 1968 article published in this *Journal*, Phelan and Orchin defined cross-conjugation as "a system possessing three unsaturated groups, two of which although conjugated to a third unsaturated center, are not conjugated to each other".[17] This definition includes a lone-pair donation from heteroatoms, as is the case in the enols of β-ketoesters and amides. Figure 6 depicts some common examples of cross-conjugated systems, where the two terminal groups are conjugated with the middle unsaturated group but not with each other. As seen in Figure 2, the lone-pair donation from the oxygen (contributor II) would attenuate the resonance stabilization of the enol (contributor I), which would also explain the decrease in enolization.

To better understand the role of these effects, density functional theory (DFT) calculations were performed to locate the optimized geometries of the keto and enol forms of **1**−**4** in their lowest-energy conformation. Selected geometrical parameters for their enols are presented in Figure 7, and a number of interesting observations can be made. First, the intramolecular hydrogen-bond distance is noticeably longer in the enol form of compounds **2**, **3**, and **4** compared to enol from the keto derivative **1**, implying that the hydrogen bond is relatively

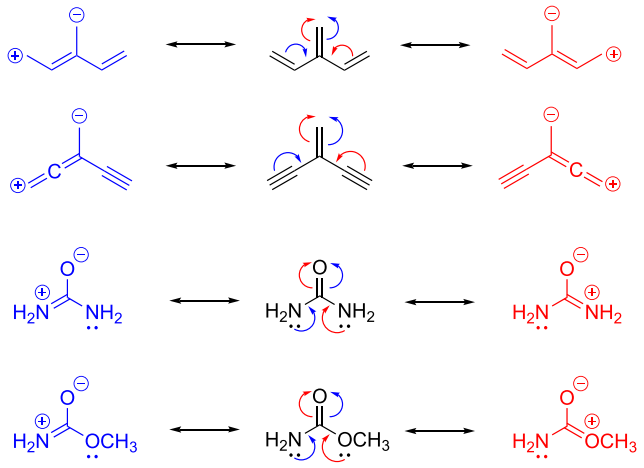

Figure 6. Examples of cross-conjugated systems.

weaker in the enol forms of compounds **2**−**4** than in the enol of species **1**. This outcome is unexpected, as a lone-pair donation (Figure 2) should increase the partial negative charge on the carbonyl oxygen in the ester group for the enol forms of **2** and **4**, thereby strengthening the intramolecular hydrogen bond. Similarly, the electron-withdrawing trifluoromethyl group is also expected to increase the −OH acidity of the enol form of **3**, which should enhance the intramolecular hydrogen bond (a more acidic proton makes a stronger hydrogen-bond donor).

However, Wiberg bond-order analysis confirms that the intramolecular hydrogen bonds are indeed weaker in the β-ketoesters **2** and **4**. Notably, the bond order of the intramolecular hydrogen bonds (indicated in square brackets in Figure 7) parallels the observed bond distance, indicating that the intramolecular hydrogen bonds are consistently weaker in the enol forms of **2**−**4** than in the enol form of **1**. Accordingly, these results suggest that intramolecular hydrogen bonding is unlikely to play a significant role in explaining the substituent effects on the enolization of these compounds.

To quantify the effect of cross-conjugation, we used an NBO analysis[13] to determine the effect of deleting the orbital interactions arising from the lone-pair resonance in the enol forms of **2** and **3**. Briefly, the NBO method expresses the electronic density in terms of a localized "Lewis" and a delocalized "non-Lewis" part. The energy of the molecule can be correspondingly divided, where the delocalized part contains contributions from the weakly occupied antibonding and Rydberg orbitals. Scheme 1 shows the calculated energies of enolization including reactions 1.3 and 1.6, where the interactions arising from the conjugation of the ester oxygen and the carbonyl π^* antibonding orbital are removed from the NBO calculations.

The data clearly indicate that, when cross-conjugation is removed, that is, deletion of resonance structure due to oxygen lone-pair donation (see reactions 1.3 and 1.6 in Scheme 1), the energies of enolization of the ketoesters **2** and **4** increase by ∼3.8 and 1.4 kcal mol^{-1}, respectively. This change is consistent with the argument that the lone-pair resonance of the ester oxygen attenuates the resonance stabilization of the enol. The effect is understandably smaller for ester **4**, as the electron-withdrawing trifluoromethyl group would "pull" the C═C π electron density away from the C═O group, thereby resulting in a smaller degree of cross-conjugation.

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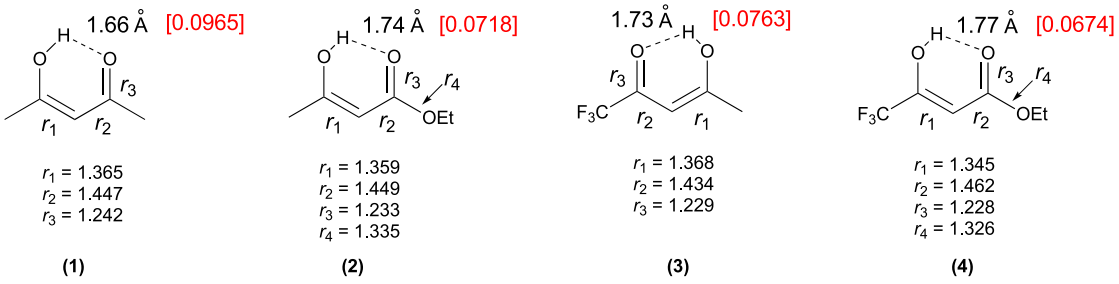
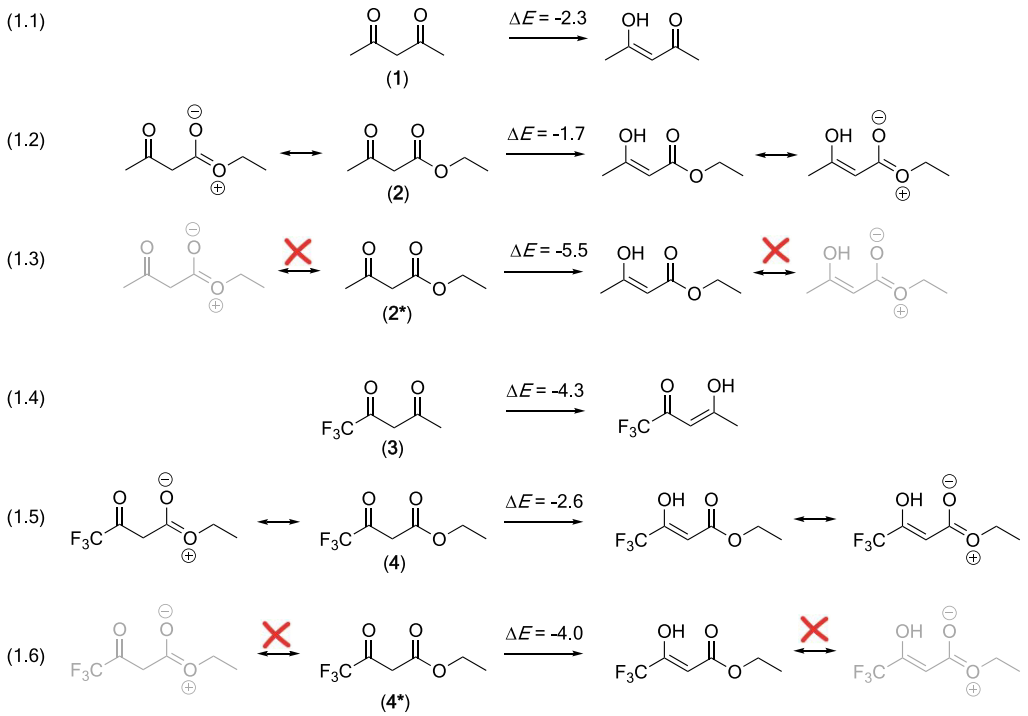


Figure 7. M06−2X/6-31G(d) optimized geometries and selected bond distances (Å) of the enols of compounds **1**−**4**. The Wiberg bond order for the intramolecular hydrogen bond is shown in square brackets (red).

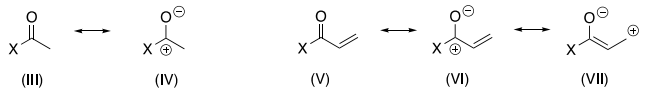
Scheme 1. Calculated Energies of Enolization (in kcal mol^{-1})[a]



[a]Reactions 1.3 and 1.6 refer to reactions where the effect of lone-pair resonance from the ester oxygen is removed.

From Scheme 1 is it also interesting to note that, when the effect of cross-conjugation is removed, the enolization of the β-ketoester **2** is predicted to be more exothermic compared to the corresponding β-diketone **1** (reaction 1.3 vs 1.1). This observation leads us to the explanation of the enol-promoting effect of electron-withdrawing groups. A number of previous studies[18,19] have indicated that electron-withdrawing groups can destabilize the keto (or, more generally, the carbonyl functional group) due to a decreased resonance stabilization. Notably, α-carbonyl electron-withdrawing substituents are expected to destabilize the resonance forms IV and VI in Scheme 2, since it is unfavorable to have an electron-withdrawing group adjacent to an electron-deficient carbon.

Scheme 2. Resonance Structures of Carbonyl-Containing Compounds



We used the isodesmic reactions shown in Scheme 3 to quantify the degree of destabilization for several different electron-withdrawing groups. The energies of reactions 3.1 to 3.3 measure the extent of destabilization (in kcal mol^{-1}) of the carbonyl group due to the electron-withdrawing substituent (CF_3, Cl, and Ph). As shown, there is a direct correlation between the strength of electron-withdrawing group (CF_3 > Cl > Ph)[20] and the extent of destabilization. Reaction 3.4 quantifies the corresponding destabilization of the carbonyl when it is conjugated with an alkene, which is ∼1 kcal mol^{-1} smaller compared to reaction 3.3. This smaller destabilization can be understood in terms of the resonance structures shown in Scheme 2 (right), where conjugation results in an additional resonance form (VII) so that the carbonyl carbon is expected to be less electron-deficient compared to the carbonyl that is not conjugated with the alkene. The 1 kcal mol^{-1} energy difference between reactions 3.3 and 3.4 is also consistent with the difference in energies of reactions 1.1 and 1.4 in Scheme 1, signifying that the enol-promoting effect of the trifluoromethyl group is due to a stronger destabilization of the keto form compared to the enol form.

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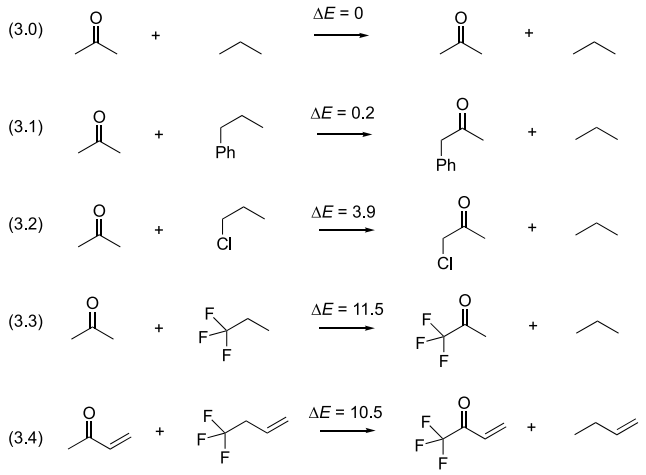
Scheme 3. Energies (in kcal mol^{-1}) of Isodesmic Reactions Illustrating the Destabilizing Effect of an Electron-Withdrawing Group Adjacent to a Carbonyl Group



Returning to the question of why the enolization of certain β-ketoesters is predicted to be more exothermic compared to their corresponding β-diketones when cross-conjugation is removed (reaction 1.3 vs 1.1 in Scheme 1), this effect is presumably because underlying the resonance effect of the ester oxygen lone-pair donation (which favors the keto) is a competing inductive effect due to the electronegativity of the same oxygen that favors the enol. Thus, when the resonance effect is absent (reaction 1.3 in Scheme 1), the enolization of β-ketoester **2** is predicted to be more energetically favorable compared to that of the corresponding β-diketone **1**.

Finally, we have also repeated the calculations (in Schemes 1 and 3) using a different density functional [B3LYP-D3(BJ)], and the results are in qualitative agreement with those obtained using M06-2X. These data, including a worked example of an NBO calculation, are provided in the Supporting Information (Tables S3 and S4 and Schemes S1 and S2) and will be useful for instructors who may wish to incorporate some of these calculations into their undergraduate experiments.

SUMMARY OF PEDAGOGICAL CONSIDERATIONS

In this study, we used β-diketones and β-ketoesters as a case study to highlight some of the challenges in presenting a straightforward explanation of substituent effects on keto−enol tautomerization to undergraduate chemistry students. In particular, there appear to be multiple factors at play in determining the difference in the position of such equilibria for different systems, including intramolecular hydrogen bonding, inductive effects, and cross-conjugation. Using experimental data from the literature and quantum-chemical calculations (*this work*), we were able to delineate the contributions of these effects to explain the substituent effects on enolization. It is envisaged that the following conclusions will enhance and deepen students' understanding of the fundamental physical organic chemistry of keto−enol tautomerization:

- Intramolecular hydrogen bonding does not appear to play an important role in explaining substituent effects on the keto−enol equilibrium positions of acyclic β-diketones and β-ketoesters.
- The enol-promoting effect of electron-withdrawing groups is due to an inductive destabilization of the carbonyl in the keto tautomer relative to the enol form.
- Electron-donating substituents (viz., β-ketoesters and amides) disfavor the enol as a result of cross-conjugation arising from a lone-pair donation from the heteroatom.
- Underlying the resonance effect associated with an electron-donating ester group (which favors the keto form), there is a competing inductive effect, where the electronegative oxygen atom in β-ketoesters destabilizes the keto form and hence favors the enol form. Quantum-chemical calculations predict that, when the effect of cross-conjugation is removed, the enolization of β-ketoesters is expected to be more favorable compared to their corresponding β-diketones.

Lastly, it is important to highlight that the present results are based on gas-phase calculations (i.e., intrinsic substituent effects), and a future direction would be to look into substituent effects in different solvents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.0c01076.

Cartesian coordinates and energies of DFT-optimized geometries, Schemes S1 and S2 calculated at the B3LYP-D3(BJ) level of theory, instructions for performing natural bond orbital analysis that might be incorporated into an undergraduate experiment (PDF)

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Notes

The authors declare no competing financial interest.

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