ARTICLES

Competing Isomerizations: A Combined Experimental/Theoretical Study of Phenylpentenone Isomerism

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The possible competition of Z/E versus hydrogen-shift isomerization in (E)-5-phenyl-3-penten-2-one (E-1) and (E)-5-phenyl-4-penten-2-one (E-2) was studied, both experimentally and theoretically. Iodine-catalyzed isomerization experiments and computational modeling studies show that the equilibrated system consists predominantly of E-1 and E-2, with E-2 in moderate excess, and with no detectable amounts of the Z (cis) diastereoisomers. Density functional theory (DFT) calculations corroborated the free energy difference ($\Delta G^{298}$ and $\Delta G_{\text{exo}}^{298}$ were −0.7 and −1.1 kcal mol$^{-1}$, respectively), and computations of Boltzmann-weighted $^1$H NMR spectra were found to be useful in confirming the assignment of the isomers. The relevance of this equilibrium to earlier work on double-bond stabilization is discussed.

Introduction

The Wittig reaction is one of the most widely used and versatile methods for the preparation of alkenes. It is well recognized that the Z/E stereoselectivity exhibited by the Wittig reaction is dependent on the nature of the substituent(s) and structure of the aldehyde and ketone, on the nature of the substituent(s) on the carbon unit and/or the phosphorus center of the organophosphorane reagent, and on the reaction conditions (solvent, temperature and base). In general, it is found that stabilized Wittig reagents favor the E-alkene products whereas nonstabilized ones favor the Z-alkene products; however, exceptions to this general rule exist. Iodine is commonly used to speed the equilibration of Z/E products, to maximize the amount of the normally thermodynamically preferred product, to promote hydrogen-shift isomerization, as well as Z/E isomerization, in the gas phase and in solution. However, it has been known since the 1960s that iodine can also promote hydrogen-shift isomerization, as well as Z/E isomerization, in the gas phase and in solution. In this connection, we are interested in predicting which molecules might be more prone to undergo hydrogen-shift equilibration rather than the desired Z/E isomerization. In a previous computational study on Z/E isomerization, many Z/E isomers had computed enthalpy differences of ~1.5 kcal mol$^{-1}$; hence, we are interested in cases where hydrogen-shift isomerization energies differ by this amount or less.

Such small hydrogen-shift energies exist in situations such as eq 1, where the substituents X and Y have similar abilities to stabilize the alkene double bond. In 1973 Hine and Flachs-Kam published a nice summary of results for disubstituted alkenes (eq 1), but the acetyl group was not tested. In 1983 Hine and Linden published another summary, based on a summary by Siroky and Prochazka, in which one end of the alkene contained gem-dimethyl groups (eq 2). Hine and Linden added data from their own equilibration, with X as the acetyl group. Their results suggest that the double-bond stabilizing ability of the acetyl group should be similar to those of nitro and cyano groups (within 0.2 kcal mol$^{-1}$), and slightly less than that of a phenyl group (by 0.8–0.9 kcal mol$^{-1}$). Thus we would expect to see hydrogen-shift equilibria in 1,3-disubstituted propanes (eq 1) where the acetyl group is paired against any of the nitro, cyano, or phenyl groups. To test the prediction, we present results for the iodine-catalyzed equilibration of (E)-5-phenyl-3-penten-2-one (E-1) and (E)-5-phenyl-4-penten-2-one (E-2), as shown in eq 3.

\[ X = CH_3, Y = CH_3 \]

\[ X = \text{Me}, Y = \text{Me} \]

\[ X = \text{Me}, Y = \text{Me} \]

\[ X = \text{Me}, Y = \text{Me} \]

\[ X = \text{Me}, Y = \text{Me} \]

\[ X = \text{Me}, Y = \text{Me} \]

\[ X = \text{Me}, Y = \text{Me} \]

\[ X = \text{Me}, Y = \text{Me} \]

\[ X = \text{Me}, Y = \text{Me} \]

The formation of the corresponding cis-isomers, Z-1 and Z-2, were also potential possibilities, both from the direct synthesis of 1 and 2 and from the iodine-catalyzed equilibration. With four potential isomers, the opportunity was taken to test the usefulness of $^1$H NMR density functional theory (DFT) calcula-
results of Boltzmann-averaged, computed \( ^1\)H NMR chemical shifts were indeed useful in isomer identification in this case. Hence, we wish to present these results in this article as well.

**Materials and Methods**

GC–MS Analysis. All GC–MS analyses were performed on a quadrupole mass spectrometer interfaced via a heated transfer line/capillary to a GC. The GC was configured with a splitless injection port and a DB-5MS fused-silica capillary column coated with a 0.25 \( \mu \)m film of stationary phase (15 m, 0.25 mm i.d.). The mass spectrometer was operated in the electron-impact ionization mode with an electron energy of 70 eV. The ion source temperature was maintained at 180 °C for all analyses, and the capillary interface transfer line was held at 250 °C. All analyses were performed using a full scan mode resulting from 2 \( \mu \)L injections. To resolve the total ion chromatograms (TIC), variable temperature programming was employed on the GC.

**Synthesis of 1 and 2.** The enone \( E-1 \) was prepared using the literature method\(^{11} \) (phenylacetaldehyde (3) with 2-(oxo- propylidene)triphenylphosphorane)\(^{11} \) to give a 44% yield of 1. A higher yielding route (Scheme 1), which involved the Horner–Wadsworth–Emmons condensation\(^{14} \) of 3 and diethyl 2-(oxopropyl)phosphonate, yielded 1 in 68% yield. In both routes for the preparation of 1, a “minor” isomer (2) that was inseparable (identical \( R_f \) as judged by tlc) from 1 was also obtained.

**(E)-5-Phenyl-4-penten-2-one (2).** A solution of phenylacetaldehyde (118 mg, 0.98 mmol) and NaH (44 mg, 60% dispersion in paraffin oil) in dry THF (3 mL) was added. The mixture was refluxed for 36 h. The cooled reaction mixture was concentrated and the residue taken into CH\(_2\)Cl\(_2\); the solution was filtered, and the filtrate was concentrated. The crude oil was purified by flash chromatography (10:1 v/v petroleum ether–Et\(_2\)O) to give 2\(^{13} \) (386 mg, 57%).

**Iodine Equilibration Studies of Enones E-1 and E-2.** Isomerization of enone 1 and isomer 2 (eq 3) was followed by \( ^1\)H NMR spectroscopy. The forward equilibration (from 1) was conducted at room temperature (23 °C) in CDCl\(_3\), and in the presence of a catalytic amount of iodine. The \( ^1\)H NMR spectrum of the mixture was taken at set intervals over a 10 day period. For the reverse equilibration (from 2), the CDCl\(_3\) solution of 2 and a catalytic amount of iodine were heated in an oil bath (53 °C) and the \( ^1\)H NMR spectrum of the mixture was taken at set intervals over 33 h, followed by standing the mixture at room temperature in the dark for two additional weeks. By the principle of microscopic reversibility, the reverse equilibration should also have proceeded at room temperature, but in two trials we did not see any change in the NMR spectrum after 2 days.

**Theoretical Methods.** Most calculations were performed with the software package Gaussian98,\(^{15} \) but the NMR calculations were performed with PQS 3.0.\(^{16} \) Geometry optimizations and frequency calculations were performed at the B3LYP/cc-pVDZ level, i.e., density functional (B3LYP)\(^{17,18} \) theory using the cc-pVDZ basis set.\(^{19} \) Better electronic energies (\( E_{\text{diss}} \)) were computed at the B3LYP/cc-pVQZ level using the B3LYP/cc-pVQZ optimized geometries. Gibbs free energies (\( G \)) for each conformer of each isomer were built by beginning with the above computed \( E \)’s and adding zero-point, thermal, and entropy corrections calculated using the rigid-rotor/harmonic-oscillator approximation and B3LYP/cc-pVDZ molecular data.

For \( ^1\)H NMR calculations, several methods were tested against a catalogued experimental 2-butenyl spectrum; we settled on the isotropic (averaged) values from the gauge-independent atomic orbital (GIAO) method\(^{20,21} \) at the B3LYP/cc-pVTZ level of theory. The zero-Kelvin calculations were performed on individual conformers at the geometries optimized as above. Chemical shifts (but not splittings) were calculated, relative to the shift for tetramethylsilane, whose absolute shift was computed to be 31.37 ppm. To account for thermal averaging...
of the contributions from several zero-Kelvin conformers, the shift $S_i$ for the $i$th H-atom was computed as a Boltzmann average of its zero-Kelvin values $S_{ij}$ from each conformer $j$:

$$S_i = \sum_j \frac{W_j S_{ij}}{\sum_j W_j}$$

The Boltzmann factors $W_j$ used the 298 K Gibbs energies $G_j$ described above and were doubled for gauche conformers to account for their double degeneracy.

**Results and Discussion**

**Equilibration Experiments.** In both the forward (from 1) and reverse (from 2) equilibrations, only two distinct isomers were detected in the $^1$H NMR spectra. The ratios of 1:2 were determined from the $^1$H NMR integrations of the methylene hydrogens. Figure 1 plots the mole fractions of $E$-2 versus time, for both experimental runs, demonstrating an equilibrium mole fraction of 0.75. This corresponds to an equilibrium constant of $K = 3.0$ and a $\Delta G_{298}^{\text{exp}}$ of $-0.7 \text{ kcal mol}^{-1}$.\(^{22}\)

In 1977, Fayos et al. reported\(^{34}\) the preparation of E-1 via the base-catalyzed elimination (DMF, Na$_2$CO$_3$) of 4-toluene-sulfinate from 5-phenyl-4-(p-toluenesulfonyl)-2-pentanone. Elimination at 60 °C resulted in a 3:1 ratio of $E$-2:$E$-1, the same ratio we observe above. Further, this ratio of $E$-2:$E$-1 was not influenced by the type of solvent used in the reactions (DMF vs CDCl$_3$). Collectively, these results confirm the prediction in the Introduction of $-0.8$ to $-0.9 \text{ kcal mol}^{-1}$ for the isomerization energy, attributed to the difference in double-bond stabilizing energy of the acetyl and phenyl groups.

**Figure 1.** Results of forward (from 1: ○) and reverse (from 2: □) equilibration experiments. Initial mole fractions of 2 were 0.08 (forward run) and 0.94 (reverse run).

**TABLE 1: Computed Relative Energies (kcal mol$^{-1}$) and Boltzmann Factors (Dimensionless) for Conformers of 1 and 2**

<table>
<thead>
<tr>
<th>isomer</th>
<th>conformer (\varphi_{Ac},\varphi_{Bz})</th>
<th>$E_{\text{elec}}$ cc-pVDZ$^c$</th>
<th>$E_{\text{elec}}$ cc-pVTZ$^c$</th>
<th>$H^{298K}$</th>
<th>$G^{298K}$</th>
<th>Boltzmann factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-1</td>
<td>I: (\varphi_{Ac},\varphi_{Bz}) = (167°,107°)</td>
<td>1.47</td>
<td>2.38</td>
<td>2.84</td>
<td>3.45</td>
<td>0.006$^c$</td>
</tr>
<tr>
<td></td>
<td>II: (\varphi_{Ac},\varphi_{Bz}) = (43°,126°)</td>
<td>4.58</td>
<td>4.14</td>
<td>4.31</td>
<td>4.51</td>
<td>0.001$^c$</td>
</tr>
<tr>
<td>Z-2</td>
<td>I: (\varphi_{Ac},\varphi_{Bz}) = (167°,155°)</td>
<td>2.23</td>
<td>2.29</td>
<td>2.38</td>
<td>2.76</td>
<td>0.010</td>
</tr>
<tr>
<td>E-1</td>
<td>IV: (\varphi_{Ac},\varphi_{Bz}) = (0°,0°)</td>
<td>1.59</td>
<td>1.30</td>
<td>1.59</td>
<td>2.04</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>III: (\varphi_{Ac},\varphi_{Bz}) = (0°,121°)</td>
<td>0.94</td>
<td>0.63</td>
<td>0.97</td>
<td>1.25</td>
<td>0.243$^c$</td>
</tr>
<tr>
<td></td>
<td>II: (\varphi_{Ac},\varphi_{Bz}) = (180°,0°)</td>
<td>0.46</td>
<td>0.69</td>
<td>0.88</td>
<td>1.22</td>
<td>0.128</td>
</tr>
<tr>
<td></td>
<td>I: (\varphi_{Ac},\varphi_{Bz}) = (180°,123°)</td>
<td>0.48</td>
<td>0.71</td>
<td>0.98</td>
<td>1.07</td>
<td>0.326$^c$</td>
</tr>
<tr>
<td>E-2</td>
<td>IV: (\varphi_{Ac},\varphi_{Bz}) = (167°,7°)</td>
<td>1.89</td>
<td>2.53</td>
<td>2.59</td>
<td>2.28</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>III: (\varphi_{Ac},\varphi_{Bz}) = (46°,110°)</td>
<td>1.10</td>
<td>0.76</td>
<td>0.90</td>
<td>0.82</td>
<td>0.502$^c$</td>
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<td></td>
<td>II: (\varphi_{Ac},\varphi_{Bz}) = (89°,117°)</td>
<td>0.56</td>
<td>0.16</td>
<td>0.40</td>
<td>0.15</td>
<td>1.562$^c$</td>
</tr>
<tr>
<td></td>
<td>I: (\varphi_{Ac},\varphi_{Bz}) = (163°,138°)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>2.000$^c$</td>
<td>0.000</td>
</tr>
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</table>

$^a$ Smaller basis set. $^b$ Larger basis set; these values were used for calculations of the enthalpy (H) and Gibbs free energy (G). $^c$ Includes factor of 2 for + gauche degeneracy ($\pm$ \(\pm 120^\circ\) possibilities for $\varphi_{Bz}$ and $\varphi_{SS}$).

**Figure 2.** B3LYP/cc-pVDZ-optimized lowest-energy conformers (conformer I in Table 1) of the four isomers of interest. Dihedral angle ($\varphi$) definitions: for 1, $\varphi_{Ac}$ = $\varphi_{1234}$, $\varphi_{Bz}$ = $\varphi_{12346}$, and for 2, $\varphi_{Ac}$ = $\varphi_{1234}$, $\varphi_{SS}$ = $\varphi_{2345}$.

**B3LYP Isomer Energies.** Geometry optimizations using B3LYP/cc-pVDZ resulted in one Z-1, two Z-2, four E-1, and four E-2 conformers; results appear in Table 1. The lowest-energy conformer (conformer I) for each isomer is shown in Figure 2. To predict equilibrium ratios of isomers, we consider the Boltzmann factor for the lowest-energy conformer of each.
isomer. If the iodine catalyst were capable only of ZIE equilibration of 1, the predicted equilibrium ratio of E-1:Z-1 would be 0.163:0.003, or 50:1 in favor of E-1. If, however, all four of these isomers appeared in equilibrium, the equilibrium ratio for E-2:Z-2:Z-1:Z-2 would be 1.000:16.0:0.01:0.003, i.e., a 6:1 ratio of E-2 to E-1 with essentially no Z-isomers. Hence, the Z isomers were not seen in the equilibration because they are too high in energy (3.5 and 4.5 kcal mol⁻¹ for Z-1 and Z-2, respectively).

From Table 1 the calculated isomer energies (based on B3LYP/cc-pVTZ electronic energies) give ΔG₂⁰₀, ΔH₂⁰₀, and ΔS₂⁰₀ values of ~0.7, ~1.0, and ~1.1 kcal mol⁻¹, respectively, for the reaction in eq 3. This is in good agreement with our experimental value of ~0.7 kcal mol⁻¹. This unexpectedly accurate computational estimate is partly fortuitous and likely benefits from excellent cancellation of errors upon taking the energy difference due to the structural similarities of E-1 and E-2.

### B3LYP ¹H NMR Spectra

The salient features in the ¹H NMR spectrum of enolized enone E-1 showed a set of olefin hydrogens centered at δ 6.05 (d) and at δ 6.88 (ddd), and the benzylic methylene doublet centered at δ 3.54. For the minor deconjugated isomer E-2, the set of olefin hydrogens resonated in the range δ 6.28 (ddd) and δ 6.46 (d), and the α-methylene hydrogens appeared as a broad doublet at δ 3.31. The assignment of E stereochemistry of the double-bond in compounds 1 and 2 is supported by the large vicinal coupling constant observed for the olefin hydrogens; in E-1, J₂₁ = 15.0 Hz and in E-2, J₂₁ = 16.0 Hz.

We used spectral modeling to make the initial identification and peak assignments of 2. Table 2 presents the zero-Kelvin chemical shifts, relative to that of T₃-symmetry tetramethylsilane, for the 11 conformers listed in Table 1. There are significant conformer effects on chemical shifts. Note that, even within one isomer like E-2, the H atoms directly attached to the C=O double bond (in bold) can be shifted up to 2 ppm depending on the particular conformation. Such effects are not seen in room-temperature spectra because of facile internal rotation. However, the data in Table 2 clearly demonstrate the sensitivity of chemical shifts to steric environment.

Boltzmann averaging over conformers resulted in four effective room-temperature stick spectra for each of the four isomers E-1, Z-1, E-2, and Z-2. These computed sets of Boltzmann-averaged proton chemical shifts, and the experimentally determined chemical shifts of the two observed isomers, E-1 and E-2, are collected in Table 3. Inaccuracies of only 0.2 ppm are seen in the computed values for E-1, which is remarkable considering the variation of H₂₃ and H₂₄ with conformer (Table 2).

The agreement for E-2 is not as good, due to the sensitive interaction between H₂₃ and an H atom on the phenyl group (H₂₄ in Table 2): the B3LYP optimization puts these too close, pushing up the chemical shifts of both these protons by roughly half a ppm. This steric problem is known in calculations on styrane: B3LYP optimizations suggest it is a planar molecule, but MP2 calculations and recent liquid-phase work¹² suggest it is nonplanar with a vinyl-phenyl torsion angle of roughly 18°. With a back-correction of 0.5 ppm to compensate, then all computed peaks again agree to within 0.2 ppm, and together with the computed energies this allowed a correct assignment of E-2. Hence, the spectrum modeling results in isomer assignments of E-1 for the main isomer and E-2 for the “growing isomer” of the forward equilibration, matching the ones suggested by the simple comparison of computed isomer energies, and ultimately confirmed by the synthesis and reverse equilibration of E-2.

### Conclusions

Iodine catalysis of the enone E-1 resulted in the formation of the positional isomer E-2, and not a simple ZIE isomerization of 1. Although enone E-1 has been described in several reports, its facile isomerization to E-2 has not been recognized until now. For enone E-1, the thermodynamic driving force for the isomerization of 1 to 2 can be attributed to the added benefit of conjugating the C=O bond to the phenyl ring rather than the carbonyl group. This benefit is experimentally determined to be ΔG₂⁰₀ = −0.7 kcal mol⁻¹ for E-1 → E-2 in chloroform as solvent.

This confirms the hypothesis, based on Hine’s tabulations,⁸⁹ that observable hydrogen-shift equilibria as depicted in eq 1 should be seen in systems where X and Y are nitro, phenyl, cyano, or acetyl groups. It also suggests that hydrogen-shift

### TABLE 2: Computed Zero-Kelvin Chemical Shifts for Every Conformer of E-2, Z-2, E-1, Z-1, Using the GIAO Method and the B3LYP/cc-pVDZ Level of Electronic Structure Theory

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<tbody>
<tr>
<td>Hᵣ₋₂₃</td>
<td>7.26</td>
<td>7.13</td>
<td>7.13</td>
<td>7.05</td>
<td>7.20</td>
<td></td>
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<td>7.27</td>
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<tr>
<td>Hᵣ₋₂₅</td>
<td>7.20</td>
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<td>Hᵣ₋₂₆</td>
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<td>Hᵣ₋₂₇</td>
<td>7.70</td>
<td>7.83</td>
<td>7.77</td>
<td>7.91</td>
<td>7.39</td>
<td></td>
<td>7.39</td>
<td>7.22</td>
<td>7.27</td>
<td>7.23</td>
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### TABLE 3: Experimental and Theoretical Chemical Shifts at 298 K

<table>
<thead>
<tr>
<th>atom²</th>
<th>expt E₁</th>
<th>theo Z₁</th>
<th>theo Z₂</th>
<th>theo E₁</th>
<th>theo E₂</th>
</tr>
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<tbody>
<tr>
<td>Hᵣ₋₂₃</td>
<td>7.2—7.4</td>
<td>7.2—7.4</td>
<td>7.20—7.98</td>
<td>7.26—7.43</td>
<td>7.22—7.40</td>
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<tr>
<td>Hᵣ₋₂₄</td>
<td>6.88</td>
<td>6.28</td>
<td>6.35</td>
<td>6.63</td>
<td>7.08</td>
</tr>
<tr>
<td>Hᵣ₋₂₅</td>
<td>6.05</td>
<td>6.46</td>
<td>6.13</td>
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<tr>
<td>Hᵣ₋₂₆</td>
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<td>3.31</td>
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<tr>
<td>Hᵣ₋₂₇</td>
<td>2.24</td>
<td>2.20</td>
<td>2.17</td>
<td>2.07</td>
<td>2.05</td>
</tr>
</tbody>
</table>

Notes:

² Notation: ph (phenyl), a (C=–C proton closest to methylene), b (C=C proton furthest from methylene), m2 (methylene), m3 (methyl).
³ Bolzmann factors (W) from Table 1.
Phenylpentenone Isomerism

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Supporting Information Available: Cartesian coordinates for conformers. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(22) Iodine increased the rate of forward equilibration 15-fold, as gauged by a second sample of E-1 left uncatalyzed for a week.