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Quantifying the Reactivity of a Remarkably Long-Lived Difluorinated Enol in Acidic Methanol via Solution Kinetics and Electronic Structure Calculations

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A simple enol acetal underwent rapid cleavage in acidic solution to generate a difluorinated enol, which was sufficiently long-lived to be characterized by 2D NMR in a protic solvent at ambient temperature. Density functional theory calculations on a model reaction suggest that there are significant differences in protonation transition state timing between the fluorinated and nonfluorinated enols.

Introduction

The relationship between enols and their aldehyde and ketone tautomers is one of the most fundamental in organic chemistry and a correct understanding of the phenomenon informs many ideas about reactions of profound synthetic importance, both in vivo and in vitro. The groundbreaking work of Capon,1 Kresge,2 and Rappoport3 developed techniques for the generation and direct observation of enols, ynois, and other reactive intermediates which tautomerize to carbonyl compounds.

A major advance was made by Capon et al.,4 who found that reactive ketene acetal 1 and ortho ester 2 hydrolyzed sufficiently rapidly for vinyl alcohol 3 to be observed in acetone–water (99:1). Relatively long-lived solutions of 3 (for example $t_{1/2}$ ca. 10 min, MeCN, 293 K) could be prepared by manipulating reaction conditions subtly. Kresge developed the laser flash photolysis technique5 to allow the direct study of a wider range of reactive intermediates in water and to reveal structure reactivity relationships. For example, enols 4 and 5 are ca. $10^2$ times ($t_{1/2}$ ca. 0.5 s) and 4 times ($t_{1/2}$ ca. 10 s) more reactive than 3 ($t_{1/2}$ ca. 35–45 s between pH 3.5 and 5.0), respectively.

Keto/enol tautomerism of aldehydes,6 acids,7 and dicarbonyl compounds8 has been studied by computational chemists. Most

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studies concentrate on the relative gas-phase energies of enol and ketone forms; the interconversion between keto and enol forms in solution and the modeling of transition states is less well explored. Dickerson and co-workers,7 and more recently, Houk and Zhang,9 studied the aldol reaction in pure water. In the latter study, the self-condensation of acetaldehyde was explained via the enol, itself formed via a facile general base and general acid catalyzed reaction, rather than via an enolate. The calculations also showed that the autoionization of water is responsible for the presence of the catalytic hydroxide and hydronium ions.

Steric and electronic effects have been enlisted to produce enols with extended lifetimes;11 the presence of electron withdrawing substituents can extend the lifetime of enols dramatically. For example, Knunyants and co-workers12 described how 6 could be stored indefinitely and distilled without significant tautomerization to the corresponding ketone 7. More recently, Burger prepared 8, and noted that it was stable under acidic conditions.13

Lemal and co-workers have also shown that perfluorination can shift the thermodynamic balance in the keto/enol tautomeric equilibrium under aprotic conditions;14 Lewis basic solvents favor the enol form of general type 10 by hydrogen bond formation to the enol hydroxyl group, and by strong destabilization of the keto-form 9. The –CO₂Me and perfluoroalkyl groups are powerfully electron withdrawing (inductively (−I) in both cases, through resonance (−R) in the former additionally) and their effects can be understood qualitatively by referring to the accepted ketonization mechanism in which general acid catalyzed protonation at carbon leads to oxacarbenium ion formation, followed by proton loss from oxygen to afford the neutral carbonyl species. Enols 6, 8, and 10 contain a −I substituent at every available position, so the difficulty of positive charge development is reasonable. The alternative ketonization mechanism involves ionization of enol to enolate followed by protonation by any available acid.15 The pKₐ values (which measure the oxygen acidities of enols) are unknown for fluorinated enols but Lemal discovered14a that a perfluoroenol was a stronger hydrogen bond donor than hexafluoro-2-propanol so fluorination should lower pKₐ, meaning that the enolate becomes available at higher acid concentrations. None of these studies allow us to predict quantitatively how a simple difluorinated enol will behave under acidic conditions, or indeed if such species can be seen at all. We wish to characterize such a species in this paper, and show via density functional calculations that its kinetic metastability arises from strong destabilization of the transition state for protonation at carbon.

Results and Discussion

During the course of a synthetic campaign, we wished to cleave difluoroalyllic alcohol 11 to hydroxyketone 12 and reduce in situ to diol 14 (Scheme 1). Exposure of 11 to acetic methanol, conditions we had developed successfully for the cleavage of MEM ((methoxy)ethoxymethyl) enol acetics16 returned crude product with a complex ¹⁹F NMR spectrum, and ultimately a crystalline solid, identified as dioxolane dimer 13 by X-ray crystallographic analysis.

We were curious about the timing of dimerization of 12, so we followed the methanolysis of 11 (in CD₃OD/Me₂SiCl) by ¹³C NMR, observing complete consumption of the starting material and the buildup of a difluoroalkenyl intermediate (either 15 or 16, clearly visible in the ¹⁹F and ¹³C NMR spectra), which decayed to 13 on a longer time scale.

Scheme 2 shows the expected mechanism for cleavage of the MEM enol acetal; the spectra indicated unambiguously that protonation at carbon cannot be the initial step, but they failed to distinguish between 15 and 16.

The critical feature distinguishing 15 and 16 is the connection between the enolic oxygen and the acetal carbon C-1′, present

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SCHEME 1. Synthesis of Dioxolane 13

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in the former and cleaved in the latter. Instead, we propose that deuteriation occurs at the enolic oxygen of 11 to afford 15 followed by C–O bond cleavage to release the difluoroenol 16, which then undergoes rate-limiting deuteriation at carbon in the acidic medium to release 17.

At the start of the reaction, the fully assigned heteronuclear multiple bond correlation (HMBC) spectrum of 11 shows a clear cross-peak (A, $^3J_{C-H}$) connecting C-2 and the diastereotopic H-1' methylene protons (Figure 1a). At 50% consumption of 11, a new C-2 type carbon is clearly visible in the $^{13}$C NMR spectrum, then later in the reaction, when 11 has been consumed completely, the HMBC spectrum (Figure 1b) shows that there is no connection between the new C-2 carbon and the acetal methylene, consistent only with cleavage of the key C–O bond and enol formation.

Solutions of 16 (L = D) could be generated by dissolving 11 in CD$_3$OD without adding any acid; for example, after 13 days, a solution of 11 in CD$_3$OD had converted completely to 16 with only trace amounts of ketonic products visible (see the Supporting Information). Presumably this reaction arises from the presence of traces of acid in the synthetic product causing cleavage of the MEM group upon storage. This corresponds to a half-life of much greater than 2 weeks at very low acid concentration ($k_o < 5 \times 10^{-7}$ s$^{-1}$). Enol formation from the enol acetal is much faster at any given acid concentration than ketonization so intermediate buildup is reasonable when the concentration of acid is very low. The measured half-life of 16 in CD$_3$OD (0.1 M in DCl, 300 K) is $1.19 \times 10^4$ s or 3.3 h; $k_{D} = 4.76 \times 10^{-4}$ M$^{-1}$ s$^{-1}$ and $k_{H} = 1.94 \times 10^{-3}$ M$^{-1}$ s$^{-1}$

$^{(17)}$ Vinyl acetals are known to undergo initial acetal hydrolysis to release the enol, followed by ketonization; see: Chang, Y.; Chwang, W. K.; Kresge, A. J.; Yin, Y. J. Am. Chem. Soc. 1989, 111, 7185.

**FIGURE 1.** Partial HMBC spectra of 11 ($^1$H 400 MHz, CD$_3$OD, 300 K): (a) 11 alone; (b) 100 min after the addition of TMS-Cl to 0.01 M. The two spectra were normalized to the same contour level, using peak B.

**SCHEME 2.** Mechanism for Cleavage of the Enol Acetal

$\text{MnCl}_2$
structures is estimated by using the polarizable continuum model (PCM). The DFT calculations were carried out with the B3LYP functional (as implemented in Gaussian98) together with a large Gaussian basis (6-311+G**()), having the necessary diffuse functions to correctly describe anions.

A recent Car—Parrinello molecular dynamics simulation of Li$^+$ and Cl$^-$ ions in liquid methanol has given an average coordination number of 3.56 for the chloride anion. We thus started with a cluster in which the Cl$^-$ was solvated by four methanol molecules, one of which was protonated. Vinyl alcohol 3 was then placed such that its $\pi$-electron density hydrogen bonded to one of the hydrogens (OH) of the protonated methanol, and the transition structure for the enol—keto transformation of 3 via an intermolecular proton shuttle route was determined. This search for the transition structure resulted in some reorganization of the starting structure to give one in which three methanol molecules were coordinated to the chloride anion, and the fourth, which is the proton acceptor, is itself hydrogen bonded to a second methanol molecule. Such a three-coordinate structure is entirely compatible with the results of MD simulations. This generic transition structure is shown in Figure 2b.

The reaction was followed from this transition structure to give the reactant and product structures shown in Figure 2a,c. All three stationary structures were properly characterized by calculation of their harmonic frequencies. In both reactant and product, the chloride anion remained three coordinate.

The calculation for the keto—enol conversion of difluorovinyl alcohol 18 was carried out starting from a transition structure similar to that for vinyl alcohol itself. Selected bond lengths and charges, together with reaction free energies and barriers for the two reactions are summarized in Figure 3.

There are considerable differences between the transition structures for the two reactions. The transition structure for the tautomerization of vinyl alcohol 3 involves very little O—H bond breaking and significant C—H bond formation, while the situation is very different for the difluoro analogue 18. Here there is considerable O—H bond lengthening and a much lower degree of C—H bond formation in the transition structure. This correlates with the considerable increase in the electron density, compared to the vinyl alcohol case, which must take place on the carbon that is accepting the proton, before such atom transfer can occur. The inductive effects of the fluorine atoms would of course be expected to acidify the OH in 16 and 18. There is also more C—C bond lengthening and C—O bond shortening in the transition structure for 18, which again reflects that O—H bond breaking is well advanced. Indeed, the transition structure for 18 more closely resembles one for enolate protonation at carbon via a hydrogen-bonded carbanion.

Both enol to keto transformations are favored energetically, that for vinyl alcohol being the more exergonic by 15 kJ mol$^{-1}$, consistent with some destabilization of the ketone by the two fluorine atoms. However, the considerable differences in the transition structures for the two reactions led to a much larger free energy barriers. The resulting value, 8 for the difluoro species 18 (67 kJ mol$^{-1}$), compared to vinyl alcohol (16 kJ mol$^{-1}$). Both the reaction free energies and barriers are little affected by the inclusion of the bulk solvent at the PCM level. We were pleased to note that despite the entropic penalty associated with the recruitment of four molecules of solvent to the cluster, the barrier calculated for the protonation of 3 is considerably lower than those calculated by Houk and Zhang for the 1,3-shift and water-catalyzed enolizations of acetaldehyde.

We may estimate the relative reaction rates of 3:18 from our free energy barriers. The resulting value, 8 x 10$^{0.1}$, is in semiquantitative agreement with our experimental estimate of 10$^6$. We have also estimated the deuterium kinetic isotope values for the two reactions within the rigid-rotor, harmonic oscillator approximation, giving values of 5.1 for the difluoro species 18 and 3.7 for vinyl alcohol 3. The experimental sKIE for 16 (L.

**FIGURE 2.** Stationary structures for enol—keto conversion: (a) enol reactant; (b) protonation transition structure; and (c) ketonic product. See Figure 3 for bond lengths.

**FIGURE 3.** Bond lengths (Å), free energies (in bold, kJ mol$^{-1}$) relative to reactant at 298 K, and atomic charges (in parentheses) for enol reactant, ketonic product, and transition structure for protonation.


(20) Tidwell has recently described a transition structure in which six water molecules link the α-carbon to an intramolecular basic group: Fedorov, A. V.; Najafian, K.; Tidwell, T. T.; Vukovic, S. Chem. 2005, 83, 1561.
That the two fluorine atoms would oppose protonation was expected, but the change in the transition structure for protonation was more of a surprise. Fluorine atoms destabilize alkenes to which they are attached (Figure 4). 21

The fluorine lone pairs are the cause of π-π repulsions (in 19 and 20), which can be relieved by pyramidalization of carbanion centers that bear them (in 21), reducing the degree of repulsive overlap. Pyramidalization also reduces the stabilizing effects of carbonyl groups on carbanions through delocalization for the same reason. 22 Hine and co-workers 23 made the original observations in this area, noting that the rate of isotopic exchange into the acidic position was lower than predicted by the Taft equation in fluoro- and methoxyacetates (the same effect also applies in the latter case). Castejon and Wiberg have carried out MP2 calculations which confirm this rationalization and support the idea that fluorine atoms acidify species which form pyramidal ions. 24 Bickelhaupt, Boche, and co-workers have shown that fluorine is more effective than the heavier halogens in this role. 25 The reorganization observed for 18 is minimizing the development of positive charge (which would be very strongly destabilized by the fluorine atoms) by re-timing the proton transfer and developing enolate character. The high acidity of the enol hydroxyl group should facilitate this reorganization; pyramidalization then minimizes destabilization by the fluorine atoms. Nevertheless, the barrier and resulting kinetic stabilization of the enol remains considerable.

We believe that the longevity of 16 is remarkable given the absence of additional electron withdrawing groups, and now wish to explore the ability of a pair of small, electronegative fluorine atoms to extend enol lifetime in biologically useful situations. 26

Experimental Section

1,1-Difluoro-2-(2-methoxyethoxymethoxy)hepta-1,6-diene-3-ol (11). n-Butyllithium (75 mmol, 32 mL of 2.40 M solution in hexane) was added dropwise to a cold (−78 °C) solution of disopropylamine (78 mmol, 9.8 mL) in dry THF (36 mL) under nitrogen. The solution was allowed to warm to −30 °C and then cooled again to −78 °C. 2-(Methoxyethoxymethoxy)-1,1-trifluoroethane 27 (36 mmol, 6.6 g) was added dropwise over 30 min to this freshly made LDA solution. The reaction was stirred at this temperature for 40 min, then 5-phenyl-1-al (42 mmol, 3.6 g) was added in one portion. The mixture was allowed to warm to −30 °C over 2 h, then quenched with NH4Cl (30 mL of a saturated aqueous solution). Water (30 mL) was added to the mixture, which was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with NaHCO3 (30 mL of a saturated aqueous solution), dried (MgSO4), and concentrated in vacuo to leave a brown oil. Kugelrohr distillation afforded aliphatic alcohol 11 (6.9 g, 78%, 100% by GC-MS) as a clear, colorless oil; bp 80−85 °C/0.25 mmHg; Rf (20% ethyl acetate in hexane) 0.34; δH (300 MHz, CDCl3) 5.80 (ddt, J = 16.7, 10.2, 6.7 Hz, 1H), 5.06−4.85 (5H, 3H), 4.24 (br, 1H), 3.96 (dd, J = 6.2, 3.6 Hz, 1H), 3.77 (dd, J = 6.2, 4.0 Hz, 1H), 3.59−3.55 (m, 2H), 3.36 (s, 3H), 2.14−2.05 (m, 2H), 1.87−1.64 (m, 2H); δF (75 MHz, CDCl3) 154.6 (dd, JF−F = 290.3, 284.3 Hz), 137.7, 118.2 (dd, JF−F = 36.4, 9.8 Hz), 115.1, 98.0, 71.4, 65.8, 65.3, 59.0, 33.1, 29.7; δF (282 MHz, CDCl3) −100.2 (dd, JF−F = 64.0 Hz, 1F), −110.0 (dd, JF−F = 64.0 Hz, JF−H = 3.8 Hz, 1F); v ms(1f/cm) = 3475 m (OH), 2932 s (CH2), 1751 w (C=CF2); m/z (EI) = 270 (52%, [M + NH4]+), 215 (10), 137 (10), 89 (100, MEM+), 89 (99, MeOCH2CH2+); HRMS (EI, M+) calculated for C11H14O2F3 252.11732, found 252.11729.

(1R*,2R*,4R*,5S*)-5-But-3-enyl-2,4-bis(difluoromethyl)-2-(1-hydroxyprop-4-enyl)-[1,13]dioxidan-4-ol (13). Trimethylsilyl chloroform (10.2 mmol, 1.30 mL) was added slowly to a solution of allyl alcohol 11 (10.0 mmol, 2.52 g) in methanol (10 mL). The solution was stirred overnight at room temperature. The solution was concentrated in vacuo to leave a clear oil that was purified by column chromatography (gradient 10% to 50% ethyl acetate in hexane) to afford dioxolane 13 (1.35 g, 82%) as a clear, colorless oil, which crystallized at low temperature (4 °C; mp 32−34 °C; Rf (20% ethyl acetate in hexane) 0.53; δH (300 MHz, CDCl3) 5.82−5.64 (5H, 2H, including 5.73 (t, JF−H = 53.7 Hz, 1H)), 5.70 (t, JF−F = 53.7 Hz, 1H), 5.07−4.89 (m, 4H), 4.65 (br s, 2H), 4.28−4.19 (m, 1H), 3.82−3.72 (m, 1H), 2.30−2.00 (m, 4H), 1.83−1.50 (m, 4H); δF (300 MHz, CDCl3) 137.5, 137.1, 115.8, 115.5, 112.8 (t, JF−F = 251.3 Hz), 112.6 (t, JF−F = 247.7 Hz), 107.15 (t, JF−F = 22.5 Hz), 100.2 (t, JF−F = 26.1 Hz), 81.0, 70.0, 29.9, 29.7, 29.4, 28.4; δF (300 MHz, CDCl3) 130.4 (dd, JF−F = 292.3 Hz, JF−F = 53.7 Hz, 1F), −132.8 (dd, JF−F = 292.3 Hz, JF−F = 53.7 Hz, JF−H = 53.7 Hz, 1F), −133.7 (dd, JF−F = 292.3 Hz, JF−F = 53.7 Hz, JF−H = 53.7 Hz, 1F), −135.5 (dd, JF−F = 292.3 Hz, JF−F = 53.7 Hz, 1F); v ms(1f/cm) = 3428 br (OH), 2931 s (CH2), 1642 s (C=C), 1073 s (C−F2; m/z (EI) = 328 (6%, M+), 310 (22, M − H2O), 300 (100, M − C2H4), Caled for C11H12O2F4: C, 51.22; H, 6.14. Found: C, 51.34; H, 6.09.

Crystal data: C11H12O2F4, crystal size 0.31 × 0.26 × 0.22 mm3, M = 164.15, monoclinic, space group P2(1)n, unit cell dimensions a = 12.8189(9) A, b = 7.7506(5) A, c = 15.7635(11) A, α = 90°, β = 94.2810(10)°, γ = 90°, V = 1561.80(18) Å3, Z = 4, Dcalcd = 1.396 Mg m−3, F(000) = 688, µ(Mo Kα) = 0.130 mm−1, T = 150(2) K, 10838 total reflections measured, 2748 independent (Rint = 0.0202), which were used in all calculations. Final R indices


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Figure 4. Orbital representations of fluorine atom π-π repulsion.
(for reflections with $I > 2\sigma(I)$) were $R_1 = 0.0362$, $\omega R_2 = 0.1626$; $R$ indices (all data) were $R_1 = 0.0387$, $\omega R_2 = 0.0954$.

**Measurement of Reaction Rates.** Alcohol **11** was exchanged (OH for OD) by evaporation from CD$_3$OD several times before use for deuteriation experiments. Reactions were initiated by the addition of TMS-Cl to a CD$_3$OD or CD$_3$OH solution of $d$-$\text{11}$ or **11**, respectively, from a microsyringe in an NMR tube which was immediately capped, sealed with film, and transferred to the probe of the NMR spectrometer. (Trifluoromethoxy)benzene was used as an internal standard.

Between 60 and 240 data points were recorded for each kinetic run. Each spectrum was automatically phased and integrated. Data were transferred to spreadsheets and normalized against the internal standard. The data fitted well to first-order plots ($R^2 = 0.999$ typically).

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**Supporting Information Available:** NMR spectra ($^1$H, $^{13}$C, $^{19}$F) for **11**, partial $^{13}$C and $^{19}$F NMR spectra during methanolysis, kinetic plots, and rate constants for methanolysis in protic and deuterated media. Cartesian coordinates, energies and atomic charges for B3LYP/6-311++G** optimized structures for ground transition, and product states for **3** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.