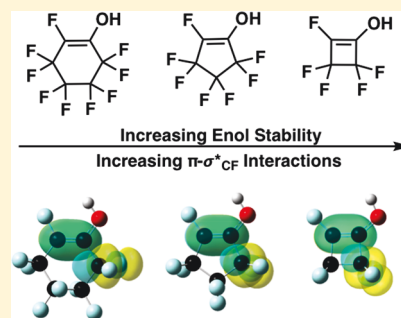


Hyperconjugative $\pi \rightarrow \sigma^*_{\text{CF}}$ Interactions Stabilize the Enol Form of Perfluorinated Cyclic Keto–Enol Systems

Brian J. Levandowski,^{†,‡} Ronald T. Raines,^{*,‡} and K. N. Houk^{*,†}[†]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States[‡]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

S Supporting Information

ABSTRACT: Lindner and Lemal showed that perfluorination of keto–enol systems significantly shifts the equilibrium toward the enol tautomer. Quantum mechanical calculations now reveal that the shift in equilibrium is the result of the stabilization of the enol tautomer by hyperconjugative $\pi \rightarrow \sigma^*_{\text{CF}}$ interactions and the destabilization of the keto tautomer by the electron withdrawal induced by the neighboring fluorine atoms. The preference for the enol tautomer further increases in smaller perfluorinated cyclic keto–enol systems. This trend is in contrast to the nonfluorinated compounds, where the enol is strongly disfavored in the smaller rings. The fluoro effect overrides the effect of the ring size that controls the equilibria in nonfluorinated compounds. The increased overlap of the enol π bond with the σ^*_{CF} orbitals of the allylic C–F bonds results in the increased preference for the enol tautomer in smaller perfluorinated keto–enol systems. We show here why the effect is much greater than in 3,3-difluorocyclooctyne.



INTRODUCTION

The enol content of simple ketones and aldehydes containing an α -hydrogen is often negligible. The equilibrium can be shifted to favor the enol tautomer if the enol is part of an aromatic system or involved in hydrogen bonding. A less conventional way to shift the equilibrium toward the enol tautomer was discovered by Lemal and Lindner when they measured the equilibrium constants for the tautomerization of the perfluorinated keto–enol systems **1–4** shown in Scheme 1.^{1–3} The perfluorination shifts the equilibrium toward the enol tautomer relative to their respective hydrogen counterparts⁴ and is especially large for smaller rings. This shift in the equilibrium has been attributed to the destabilization of the ketone through the electron withdrawal induced by the neighboring fluoro groups.⁵ Lemal and Lindner studied computationally the optimized structures of **2–4** to understand why the propensity for the enol tautomer increases as the ring size of the perfluorinated cyclic keto–enol systems decreases.⁶ They noted that the distance between the vinyl and allylic fluorine atoms increases as the ring size of the perfluorinated cyclic enol systems becomes smaller, and they attributed the increased presence of the enol tautomer to the weaker fluorine–fluorine steric repulsions in smaller cyclic systems.

We have studied computationally the perfluorinated cyclic keto–enol systems and find that the hyperconjugative interactions between the π and σ^*_{CF} orbitals stabilize the perfluorinated enols and increase significantly as the ring size decreases. We predict that this hyperconjugative effect and the preference for the enol tautomer become even larger in three-membered rings.

COMPUTATIONAL METHODS

The geometries were optimized with an M06–2X⁷ functional and a 6-31G(d) basis set in Gaussian 09, Revision D.01.⁸ The single-point energies were calculated with a larger 6-311++G(d,p) basis set and an implicit SMD⁹ solvation model with carbon tetrachloride (CCl₄) as the solvent. The Natural Bond Orbital (NBO 3.1)¹⁰ analysis at an M06–2X/6-31G(d) level of theory was used to quantify the strength of the donor–acceptor orbital interactions.

RESULTS AND DISCUSSION

The computed reaction energies (ΔG) for the tautomerizations of **1–10** from the keto to the enol form are reported in Figure 1. In agreement with the experimental work of Lemal and Lindner,^{1–3} the perfluorinated acyclic keto–enol system has the lowest preference for the enol tautomer, and the thermodynamic preference for the enol form in the perfluorinated cyclic systems (**2–5**) increases with decreasing ring size. The hydrogen counterparts (**7–10**) show the opposite trend, where the formation of the enol tautomer becomes increasingly unfavorable with decreasing ring size. This trend has been attributed to the differences in the ring strain of the exocyclic and endocyclic double bonds.¹¹ The perfluorination of the acyclic keto–enol system shifts the equilibrium by 5 kcal/mol. This shift in equilibrium toward the enol tautomer upon fluorination increases as the ring size of the perfluorinated cyclic keto–enol systems decreases and is largest for the three-membered cyclic keto–enol system with a shift of 24 kcal/mol.

Received: March 24, 2019

Published: April 16, 2019



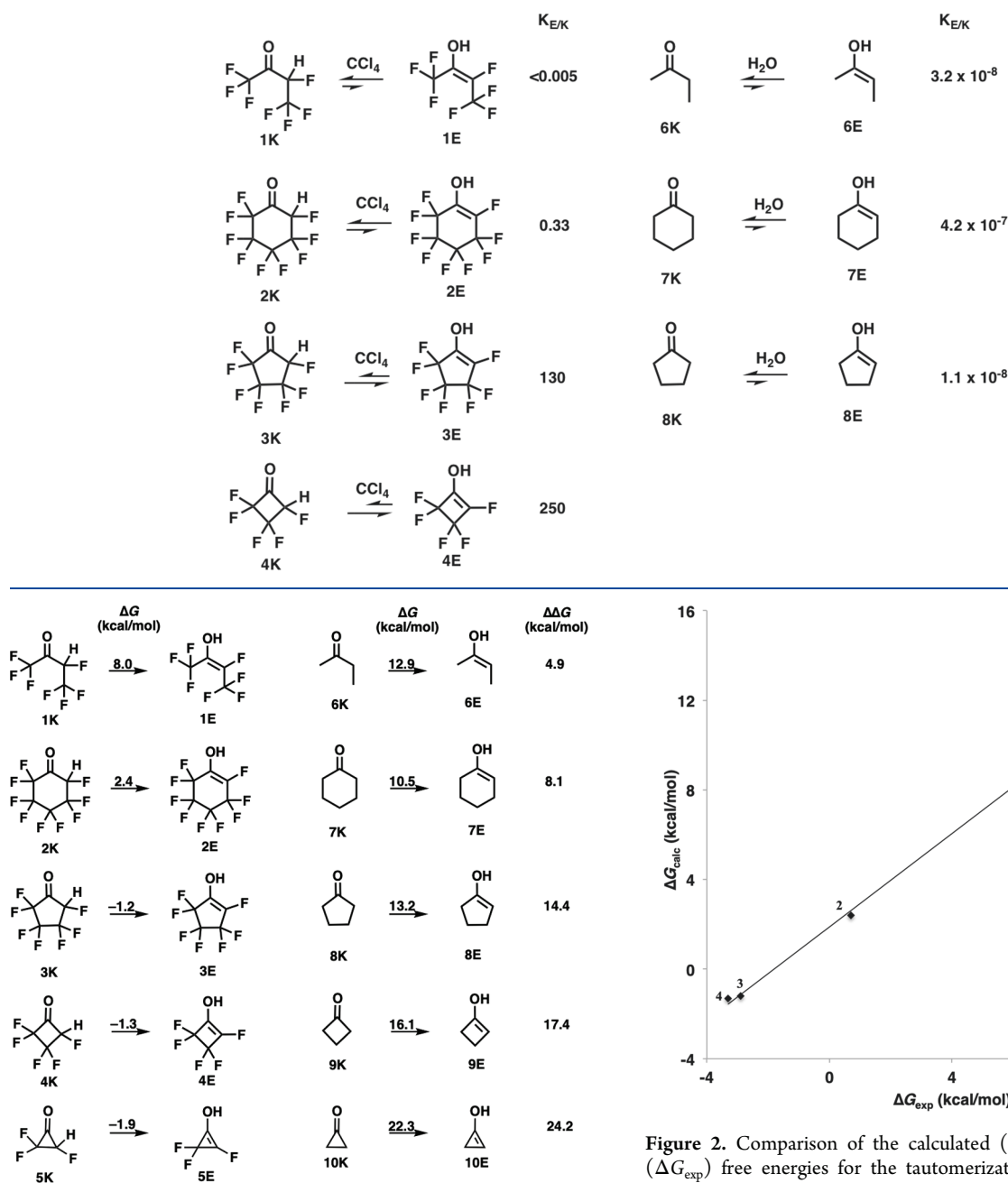
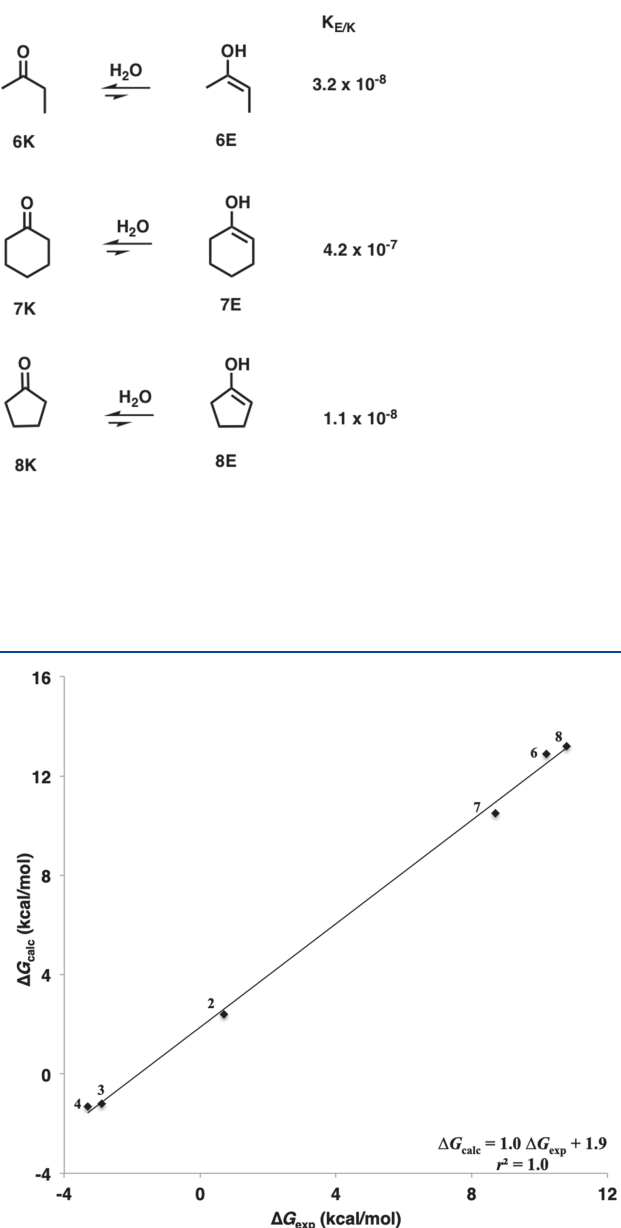
Scheme 1. Experimental Equilibria for the Keto–Enol Tautomerization of the Perfluorinated^{1–3} and Hydrocarbon⁴ Keto–Enol SystemsFigure 1. Computed reaction energies (ΔG) for the keto–enol tautomerizations of keto–enol systems 1–10.

Figure 2 shows a plot of the calculated free energies against the free energies from the experimentally measured equilibrium constants. The trend in the experimental free energies is qualitatively reproduced in the computed free energies, although the stability of the enol form is systematically underestimated by about 2 kcal/mol for each system.

Equations 2–5 in Figure 3 for the analogous hydrocarbon systems measure the strain of the endocyclic double bond relative to the exocyclic double bond. Equation 1 serves to show that there is a 2 kcal/mol bias for the endocyclic double bond when the strain is not important, because the endocyclic alkene is more substituted and more stabilized by hyper-

Figure 2. Comparison of the calculated (ΔG_{calc}) and experimental (ΔG_{exp}) free energies for the tautomerization of the perfluorinated and hydrocarbon keto–enol systems.

conjugation relative to the exocyclic alkene. There is a 2–3 kcal/mol preference for the endocyclic double bond in the five- and six-membered rings. For the four-membered ring, the endocyclic and exocyclic double bonds are similar in energy. The significant strain of the endocyclic double bond in the three-membered ring results in a preference of 11 kcal/mol for the exocyclic double bond.

The isodesmic equations 6–10 in Figure 4 measure the effect of fluorine substitution on the stability of the ketones relative to fluorinated alkanes. These isodesmic equations show that fluorine substitution destabilizes the ketones. The three-membered ketone is the least destabilized by the fluorine substitution, with a value of 19 kcal/mol in the isodesmic equation. The other perfluorinated cyclic ketones 2–4 and the

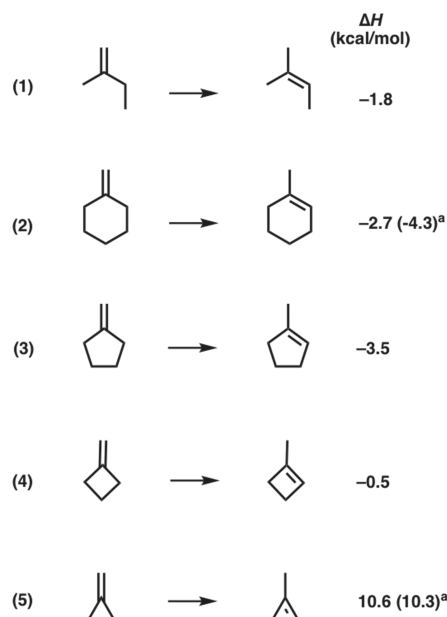


Figure 3. Isodesmic equations 2–5 measure the stability of an endocyclic double bond relative to an exocyclic double bond. Equation 1 compares the stability of a trisubstituted alkene relative to a disubstituted alkene. ^aFrom the experimental heats of formation.¹²

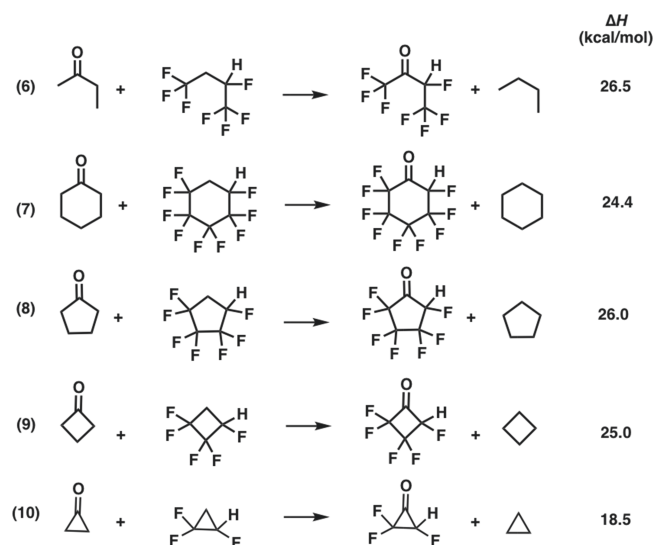


Figure 4. Isodesmic equations 1–5 measure the effect of fluorine substitution on the stability of a ketone.

perfluorinated acyclic ketone **1** are destabilized to a larger extent with destabilization energies ranging from 29 to 27 kcal/mol. Although the simple conclusion is that an electron-withdrawing carbonyl is destabilized by electron-withdrawing CF bonds, this does not rationalize the general trend of the increasing enol preference as the ring sizes decrease.

The isodesmic equations 11–15 in Figure 5 measure the strength of the hyperconjugative interactions between the π bond and the allylic σ^*_{CF} acceptors. The $\pi \rightarrow \sigma^*_{CF}$ hyperconjugative interactions are least stabilizing for the acyclic system and become more stabilizing as the cyclic systems become smaller. The trend in the strength of the $\pi \rightarrow \sigma^*_{CF}$ hyperconjugative interactions parallels the trend in the computed thermodynamic stabilities of the perfluorinated

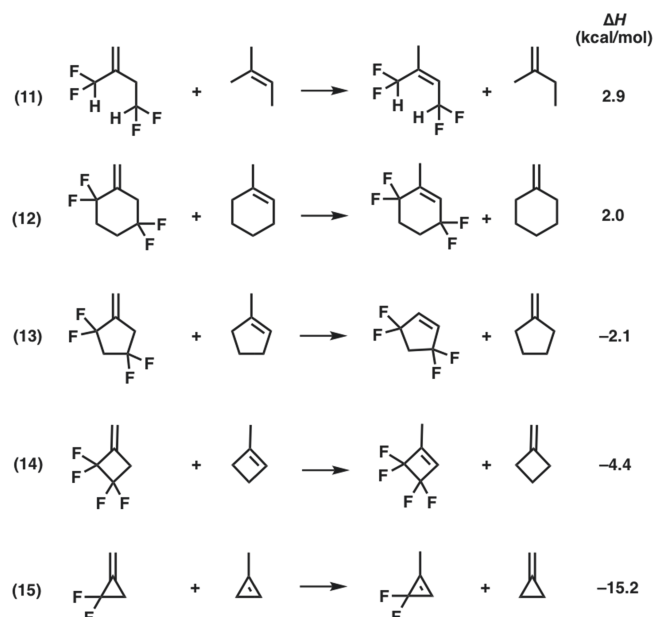


Figure 5. Isodesmic equations 11–15 estimate the strength of the $\pi \rightarrow \sigma^*_{CF}$ hyperconjugative interactions.

Table 1. Computed Strengths of the $\pi \rightarrow \sigma^*_{CF}$ Interaction (kcal/mol) for Enols 1–5

	1E	2E	3E	4E	5E
$\pi \rightarrow \sigma^*_{CF}$					
$\pi-\sigma^*_{F1}$	0.9	7.5	5.3	8.6	33.4
$\pi-\sigma^*_{F2}$	6.2	3.9	8.4	8.6	33.4
$\pi-\sigma^*_{F3}$	2.3	9.5	10.1	9.7	
$\pi-\sigma^*_{F4}$	2.6	4.9	6.5	9.7	
$\pi-\sigma^*_{F5}$	8.1				
$\pi-\sigma^*_{F6}$	1.5				
total	21.6	25.8	30.3	36.6	66.8

Table 2. Preorthogonalized NBO Overlap Integrals in Atomic Units for the $\pi \rightarrow \sigma^*_{CF}$ Interactions

	1E	2E	3E	4E	5E
$\pi \rightarrow \sigma^*_{CF}$					
$\pi-\sigma^*_{F1}$	0.08	0.22	0.19	0.25	0.34
$\pi-\sigma^*_{F2}$	0.21	0.16	0.23	0.25	0.34
$\pi-\sigma^*_{F3}$	0.14	0.23	0.24	0.25	
$\pi-\sigma^*_{F4}$	0.13	0.17	0.19	0.25	
$\pi-\sigma^*_{F5}$	0.22				
$\pi-\sigma^*_{F6}$	0.10				
average	0.15	0.20	0.21	0.25	0.34

enols in Figure 1. This correlation suggests that the increase in the preference for the enol tautomer in smaller perfluorinated cyclic keto–enol systems is related to the increase in the strength of the $\pi \rightarrow \sigma^*_{CF}$ hyperconjugative interactions in smaller perfluorinated cyclic enols. The absence of the vinyl

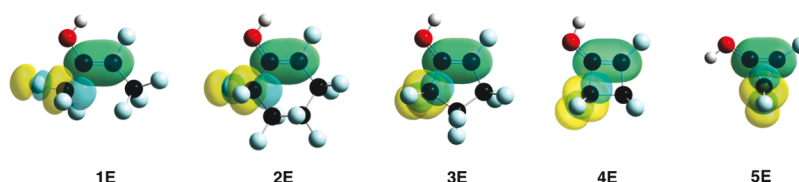


Figure 6. Top view of a $\pi \rightarrow \sigma^*_{\text{CF}}$ interaction in the enol forms of 1–5.

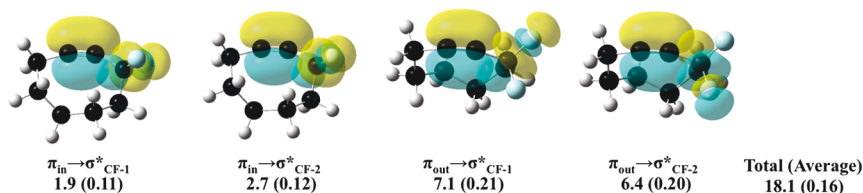


Figure 7. Strength in kcal/mol and overlap in parenthesis for the $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interactions in DIFO.

fluorine atom in isodesmic equations 11–15 also shows that the trend in the keto–enol equilibrium of the perfluorinated keto–enol systems is not related to steric effects between the vinyl and allylic fluorine atoms.

The strength of each $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interaction in the perfluorinated enol systems was quantified by the NBO calculations and is listed in Table 1. The trend in the thermodynamic stability of the perfluorinated enols relative to the keto tautomer parallels the strength of the $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interactions, which are weakest in the perfluorinated acyclic enol and become increasingly stabilizing as the perfluorinated cyclic enol ring becomes smaller. The individual $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interactions range from 1 to 8 kcal/mol in the perfluorinated acyclic enol. For the four- to six-membered perfluorinated cyclic enols 2E to 4E, the hyperconjugative interactions are generally stronger and range from 4 to 10 kcal/mol. The $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interactions are significantly stronger for the three-membered perfluorinated cyclic enol 5E at 33 kcal/mol per interaction. In addition to the factors that will be mentioned later, this system gains a significant stabilization from the hyperconjugative aromaticity.^{13,14}

The analysis of the preorthogonalized NBO overlap integrals of the π and σ^*_{CF} orbitals reveals that the increase in the strengths of the $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interactions in smaller perfluorinated cyclic enols is a result of the better orbital overlap between the π and σ^*_{CF} orbitals (Table 2). To show how the orbital overlap increases across the perfluorinated enol series, a $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interaction for each of the perfluorinated enols is depicted in Figure 6. The allylic C–F bonds rotate increasingly inward, closer to the remote end of the double bond, as the ring size of the perfluorinated enol decreases. This inward movement increases the overlap of the σ^*_{CF} orbitals with the π orbital region of highest electron density. In turn, this greater overlap results in more stabilizing $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interactions.

A related overlap effect has been reported in Diels–Alder reactions of cycloalkenes, where the inward motion of the cycloalkene allylic C–H bonds results in an increased overlap of the highest occupied molecular orbital (HOMO) of the cycloalkene with the lowest unoccupied molecular orbital (LUMO) of the diene.¹⁵ This increased overlap contributes to cyclopropene being over a million times more reactive than cyclohexene in the inverse electron-demand Diels–Alder

reaction with 3,6-(bistrifluoro)-tetrazine¹⁶ and to the unusually large *endo* preference.¹⁴

The “negative” hyperconjugative effect of CF bonds is well known.¹⁷ A computational investigation by Alabugin et al. showed that $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interactions of the in-plane (π_{in}) and out-of-plane (π_{out}) π -systems with the propargylic fluorine atoms not only stabilize the ground state of difluorocyclooctyne (DIFO) but also increase the reactivity of this molecule in cycloadditions by stabilizing the transition state even more.¹⁸ The hyperconjugative interactions of the in-plane and out-of-plane π orbitals with the σ^*_{CF} orbitals of DIFO are shown in Figure 7, with the strength of the hyperconjugative interactions in kcal/mol and the preorthogonalized NBO overlap integral listed below each interaction. The $\pi \rightarrow \sigma^*_{\text{CF}}$ interactions in DIFO with overlap integrals of 0.1 to 0.2 are weaker than the $\pi \rightarrow \sigma^*_{\text{CF}}$ interactions in the perfluorinated cyclic enols studied by Lemal and Lindner with overlap integrals of 0.2 to 0.3. The strength of the $\pi \rightarrow \sigma^*_{\text{CF}}$ interactions in cyclic systems is determined by the ring size, and the overlap integrals of the π and σ^*_{CF} orbitals in the eight-membered ring of DIFO are less favorable than in smaller six- to three-membered rings. The increased overlap of the $\pi \rightarrow \sigma^*_{\text{CF}}$ interactions in smaller cyclic systems results in stronger $\pi \rightarrow \sigma^*_{\text{CF}}$ interactions and consequently greater chemical effects.

Hyperconjugative interactions of the C_3 cyclopropene substituents with the alkene π orbitals have been shown to induce aromatic or antiaromatic properties depending on the electronic nature of the substituents.^{13,14} Hyperconjugative acceptors stabilize the cyclopropene through aromatic 2-electron cyclic delocalization, whereas donors like alkyl or silyl substituents destabilize the cyclopropene with antiaromatic 4-electron delocalization. The unusually high strength of the $\pi \rightarrow \sigma^*_{\text{CF}}$ hyperconjugative interactions in the three-membered perfluorinated enol results from the increased overlap of the π and σ^*_{CF} orbitals that leads to a 2π electron hyperconjugative aromaticity.

CONCLUSIONS

The shift of keto–enol equilibrium in perfluorinated systems toward the enol tautomer arises from the hyperconjugative $\pi \rightarrow \sigma^*_{\text{CF}}$ interactions of the enol π bond with the allylic C–F bonds and the destabilization of the keto tautomer through electron withdrawal by the electronegative fluorine atoms. The equilibrium increasingly favors the enol tautomer for smaller

rings, because the increased overlap of the π and σ^*_{CF} orbitals in smaller perfluorinated cyclic keto–enol systems results in an increased negative hyperconjugative stabilization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00825.

Cartesian coordinates and energies of all optimized structures are available in the Supporting Information (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: rtraines@mit.edu (R.T.R.).

*E-mail: houk@chem.ucla.edu (K.N.H.).

ORCID

Brian J. Levandowski: 0000-0002-8139-9417

Ronald T. Raines: 0000-0001-7164-1719

K. N. Houk: 0000-0002-8387-5261

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation (no. CHE-1764328) and the National Institute of Health (no. R01 GM044783) for the financial support of this research. The computational resources were provided by the UCLA Institute for Digital Research and Education (IDRE). This work used the Extreme Science and Engineering Discovery Environment (XSEDE),¹⁹ which is supported by the National Science Foundation grant number ACI-1548562.

■ REFERENCES

- (1) Lindner, P. E.; Lemal, D. M. Highly Fluorinated Cyclopentanones and Their Enols. *J. Org. Chem.* **1996**, *61*, 5109–5115.
- (2) Lindner, P. E.; Correa, R. A.; Gino, J.; Lemal, D. M. Novel Keto–Enol Systems: Cyclobutane Derivatives. *J. Am. Chem. Soc.* **1996**, *118*, 2556–2563.
- (3) Lindner, P. E.; Lemal, D. M. Perfluorinated Cyclic and Acyclic Keto–Enol Systems: A Remarkable Contrast. *J. Am. Chem. Soc.* **1997**, *119*, 3259–3266.
- (4) Keeffe, J. R.; Kresge, A. J.; Schepp, N. P. Keto–Enol Equilibrium Constants of Simple Monofunctional Aldehydes and Ketones in Aqueous Solution. *J. Am. Chem. Soc.* **1990**, *112*, 4862–4868.
- (5) (a) Lemal, D. M. Perspective on Fluorocarbon Chemistry. *J. Org. Chem.* **2004**, *69*, 1–11. (b) Khalil, S. M. A DFT study on the stepwise fluorinated methylenecyclopropane $\rightleftharpoons$ 1-Methylcyclopropene system. *Z. Naturforsch. A* **2008**, *63*, 42–48.
- (6) Lindner, P. E.; Lemal, D. M. Energetics of Fluoroalkene Double Bond Isomerizations. *J. Am. Chem. Soc.* **1997**, *119*, 3267–3273.
- (7) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
- (8) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; et al. *Gaussian 09*; Revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.
- (9) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric

Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

(10) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*; Version 3.1. Gaussian Inc.: Pittsburgh, 2003.

(11) (a) Conn, J. B.; Kistiakowsky, G. B.; Smith, E. A. Heats of Organic Reactions. VIII. Some Further Hydrogenations, Including Those of Some Acetylenes. *J. Am. Chem. Soc.* **1939**, *61*, 1868–1876. (b) Houk, K. N.; Jabbari, A.; Jr Hall, H. K.; Alemán, C. Why Delta-Valerolactone Polymerizes and Gamma-Butyrolactone Does Not. *J. Org. Chem.* **2008**, *73*, 2674–2678.

(12) Pedley, J. B.; Naylor, R. D.; Kirby, S. P. *Thermochemical Data of Organic Compounds*; 2nd ed., Chapman and Hall: London, 1986, Table 1.1.

(13) Fernández, I.; Wu, J. I.; Schleyer, P. von R. Substituent Effects on “Hyperconjugative” Aromaticity and Antiaromaticity in Planar Cyclopolyenes. *Org. Lett.* **2013**, *15*, 2990–2993.

(14) Levandowski, B. J.; Houk, K. N. Hyperconjugative, Secondary Orbital, Electrostatic, and Steric Effects on the Reactivities and Endo and Exo Stereoselectivities of Cyclopropene Diels–Alder Reactions. *J. Am. Chem. Soc.* **2016**, *138*, 16731–16736.

(15) Levandowski, B. J.; Hamlin, T. A.; Bickelhaupt, F. M.; Houk, K. N. Role of Orbital Interactions and Activation Strain (Distortion Energies) on Reactivities in the Normal and Inverse Electron-Demand Cycloadditions of Strained and Unstrained Cycloalkenes. *J. Org. Chem.* **2017**, *82*, 8668–8675.

(16) Thalhammer, F.; Wallfahner, U.; Sauer, J. Reaktivität Einfacher Offenkettiger Und Cyclischer Dienophile Bei Diels–Alder–Reaktionen Mit Inversem Elektronenbedarf. *Tetrahedron Lett.* **1990**, *31*, 6851–6854.

(17) (a) Kos, A. J.; Schleyer, P. von R. The importance of negative (anionic) hyperconjugation. *Tetrahedron* **1983**, *39*, 1141–1150. (b) Alabugin, I. V.; dos Passos Gomes, G.; Abdo, M. A. Hyperconjugation. *WIREs Comput. Mol. Sci.* **2019**, *9*, No. e1389.

(18) Gold, B.; Shevchenko, N. E.; Bonus, N.; Dudley, G. B.; Alabugin, I. V. Selective Transition State Stabilization via Hyperconjugative and Conjugative Assistance: Stereoelectronic Concept for Copper-Free Click Chemistry. *J. Org. Chem.* **2011**, *77*, 75–89.

(19) Towns, J.; Cockerill, T.; Dahan, M.; Foster, I.; Gaither, K.; Grimshaw, A.; Hazlewood, V.; Lathrop, S.; Lifka, D.; Peterson, G. D.; et al. XSEDE: Accelerating Scientific Discovery. *Comput. Sci. Eng.* **2014**, *16*, 62–74.