Correlation Effects on Intramolecular C-H...OH and O-H...O Hydrogen Bond Interactions in Azelaic Acid: an ab initio study

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Acknowledgements

Correlation effects on intramolecular C-H…OH and O-H…O hydrogen bond interactions in azelaic acid: An *ab initio* study

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ABSTRACT Electron correlation effects on both conventional, O-H…O, and nonconventional, C-H…O, intramolecular hydrogen bonds present in a selected azelaic acid folded conformation were evaluated *ab initio* using HF and MP2 methodologies. The relative strength of the hydrogen bonds was examined through different indicators derived from geometry, vibrational frequencies, and electron density along the hydrogen bond path. The HF method results in weaker O-H…O and C-H…O hydrogen bonds when compared with the corresponding results using the MP2 method. Additionally, the stability of the folded azelaic conformation is found to depend on the level of theory used. Accordingly, the zero-point corrected energies of the folded conformation relative to a linear conformation are calculated to be +4.46 kcal/mol and -3.67 kcal/mol at the HF and MP2 levels of theory respectively. The positive sign at the HF level indicates that the folded conformation is less stable than the linear conformation, in sharp contrast to the MP2 method, which predicts the folded conformation to be preferred.

INTRODUCTION

Nonanedioic acid, more commonly known as azelaic acid ($C_9H_{16}O_4$), is a dicarboxylic acid that naturally forms in the atmosphere and originates from photo oxidation of biogenic and anthropogenic compounds as well as direct emissions (Bilde, 2003). Azelaic acid has a vast variety of uses within multiple fields. It is currently used as an ingredient for whole grain cereals, rye, barley, and animal products as well as a key component of anti-inflammatory medication particularly for acne and rosacea (National Center for Biotechnology Information Staff, 2021).

In an ongoing computational investigation of the gas phase stability of azelaic acid, we found several conformations that are stabilized by both conventional O-H…O and unconventional C-H…O hydrogen bonds.

According to the International Union of Pure and Applied Chemistry (IUPAC), a hydrogen bond is defined as "an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X-H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation" (Arunan et al., 2011). However, further investigation has revealed that the criteria for a hydrogen bond is

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much more flexible than previously thought. One such exception to the traditional definition is the unconventional C-H…O hydrogen bond. Although significantly weaker than conventional hydrogen bonds, C-H…O falls within the range of accepted hydrogen-bond angles, lengths, and stabilization energies (Desiraju & Steiner, 1999).

Accurate description of noncovalent interactions in computational chemistry depends on the extent to which the computational method employed accounts for electron correlation. Physically, this phenomenon arises because the motion of an electron correlates (rather than being independent) to the motion of all other electrons in the molecule. In the case of molecular orbital theory, the quality of the basis set used to construct the molecular wave function also plays a role in the accuracy of the results. The larger and more flexible the basis set, the more accurate the description (Grimme et al., 2016).

In this study, the effects of electron correlation on the description of intramolecular C-H…O and O-H…O hydrogen bonds are examined using one specific folded conformation of azelaic acid in the gas phase. An inherent deficiency of the Hartree-Fock, HF, method is its representation of the molecular wave function using a single determinant. Accordingly, applying the HF method results in the electronic configuration of the ground state energy. Although a single determinant accounts partly for the correlation of the motions of electrons with the same spin, it does not account for the correlation between electrons with opposite spin. Methods that improve upon the treatment of the correlation between motions of electrons are known as electron correlation methods or post-HF methods. Among the many post-HF methods, the MPn method, uses perturbation theory to better account for electron correlation. In principle, increasing the order of perturbation, n, improves the account of electron correlation (Cramer, 2009). In particular, the second order perturbation approach, MP2, is widely recognized to be a method of choice because of its good balance between accuracy and computational cost (Khire et al., 2018). In fact, the computational execution time cost in a quantum mechanical energy calculation typically scales with the number of

basis functions, N, as O(N^3) for HF, O(N^5) for MP2, and O(N^7) for CCSDT (which is considered the gold standard among *ab initio* methods). Thus, in this work, we use the MP2 method to improve upon the HF method results using a large basis set (447 basis functions in the monomer of azelaic acid).

METHODS

Gas phase geometry optimizations and frequency calculations on a selected conformation of azelaic acid were performed with the HF and the MP2 molecular orbital methods along with the 6-311+G(2d,p) basis set. The Gaussian 16 package of programs was used for these calculations (Frisch et al., 2016). The magnitude of the electron density accumulated at the critical points along the path of the O-H…O and C-H…O hydrogen bonds were obtained using the AIMALL software package (Keith, 2013).

The structure of azelaic acid for this study was selected from an initial exploration of the potential energy starting at a linear conformation of the monomer and within an energy window of 5.25 kcal/mol. The MMF94 force field, as implemented in the program GMMX, was employed for the search. The GMMX program is an add-on for Gauss View 6 which adds the ability to perform conformational searches from within Gauss View (Dennington et al., 2016).

A detailed discussion of the conformational search results and the effects of solvation on conformational stability of azelaic acid will be published elsewhere.

RESULTS

Electron correlation effects on the description of conventional O-H…O and unconventional C-H…O hydrogen bonds in a selected azelaic acid conformation were examined. The presence of C-H…O hydrogen bond as a stabilizing force was somewhat unexpected given that it is a relatively weak interaction, certainly much weaker than a conventional hydrogen bond, i.e., O-H…O.

Correlation effects were examined by comparing structural or geometrical parameters obtained from the HF and MP2 methods respectively. Additionally, harmonic vibrational frequencies corresponding to the stretching of the hydrogen bond donors (C-H and O-H respectively) were examined. Lastly, the electron density accumulated at the critical points along the hydrogen bond paths was also considered for assessing correlation effects.

For ease of later discussion, the optimized initial linear conformation of azelaic acid is shown in Figure 1 below.
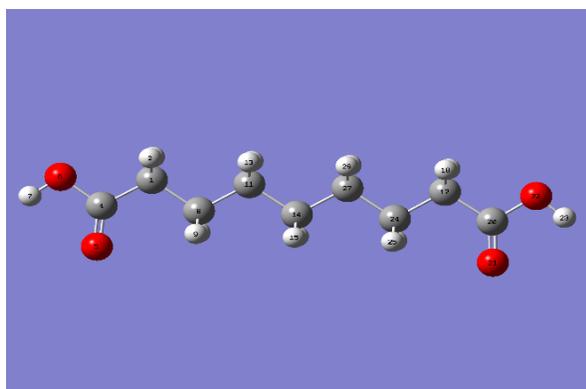
Figure 1: MP2/6-311+G(2d,p) optimized linear conformation of azelaic acid. Oxygen in red, carbon in dark grey, and hydrogen in light grey.

The overall shape of the optimized folded conformation of azelaic acid is shown in Figure 2 below.
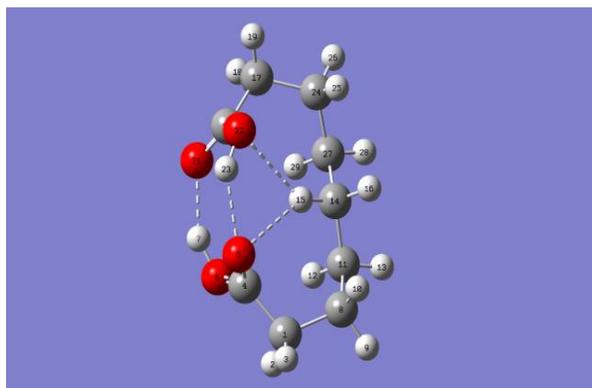
Figure 2: MP2/6-311+G(2d,p) optimized azelaic acid folded conformation in the gas phase. Oxygen in red, carbon in dark grey, and hydrogen in light grey. Covalent bonds are represented with solid lines and hydrogen bonds with dashed lines.

Table 1 displays a summary of relevant geometrical parameters for the optimized folded azelaic monomer. The geometrical parameters follow the atomic number labels detailed in Figure 2.

Geometrical Parameter	HF	MP2
R(O6-H7)	0.953	0.988
R(O22-H23)	0.952	0.985
R(C14-H15)	1.078	1.088
R(O6-H7…O21)	2.030	1.776
R(O22-H23…O5)	2.398	1.953
R(C14-H15…O22)	2.542	2.414
R(C14-H15…O5)	2.556	2.437
A(O6-H7…O21)	144.1	150.8
A(O22-H23…O5)	134.6	146.4
A(C14-H15…O22)	139.2	140.9
A(C14-H15…O5)	145.4	147.9
D(C14-H15…O5…O22)	173.2	179.6

Table 1: Relevant geometrical parameters of folded azelaic acid optimized using the HF and MP2 Methods and 6-311+G(2d,p) Basis Set. Bond distances in Angstroms, angles in degrees.

Table 2 shows the harmonic vibrational frequencies associated with the stretching of the covalent O-H and C-H bonds of the hydrogen bond donors. Also shown in Table 2 are the corresponding percent changes in the calculated densities resulting from correlation effects.

	Frequency		% Change
			MP2 relative
Stretching mode	HF	MP2	to HF
ν(O22-H23)	4035	3539	-12
ν(O6-H7)	3995	3457	-13
ν(C14-H15)	3292	3188	-3

Table 2: Selected harmonic vibrational stretching frequencies (ν, in cm^{-1}) of folded azelaic acid using the HF and MP2 Methods and the 6-311+G(2d,p) basis Set.

Lastly, Table 3 shows the electron densities accumulated at the critical points defining the hydrogen bond interaction of the optimized folded conformation of azelaic acid. Also shown

in Table 3 are the corresponding percent changes in the calculated densities resulting from correlation effects.

Electron Density, ρ_c (a.u.)	HF	MP2	% Change (MP2 relative to HF)
ρ(O6-H7…O21)	0.018	0.035	94
ρ(O22-H23…O5)	0.009	0.024	167
ρ(C14-H15…O22)	0.009	0.012	33
ρ(C14-H15…O5)	0.010	0.013	30

Table 3: Electron density at a given hydrogen bond critical point (in atomic, a.u., units) found in folded azelaic acid using both the HF and MP2 methods each with the 6-311+G(2d,p) Basis Set.

In chemistry, a bond is typically defined as the force responsible for holding together the atoms in a compound. The conceptual representation of this definition varies, however, with the theoretical model used to describe bonding (Tro, 2017). In particular, the theoretical foundation for using electron densities as a measure of bond strength stems from the quantum theory of atoms in molecules, QTAIM, which characterizes a bond between a pair of atoms in terms of the topology of the electron density along the bond-line path connecting the atoms (Bader, 1990). Specifically, the existence of a bond critical point (that is, the point where the gradient of the density is zero) provides evidence of the existence of a bond, whereas its absence indicates the lack of bonding. According to the QTAIM, the value of the electron density at the bond critical point, ρ_c, directly correlates with the strength of the bond.

DISCUSSION

Inspection of Figure 2 reveals the presence of two conventional O-H…O hydrogen bond interactions through the carboxylic acid motifs. Additionally, the presence of two C-H…O hydrogen bonds is also apparent in Figure 2. The C-H…O hydrogen bonds constitute what is known as a bifurcated hydrogen bond wherein the hydrogen atom is shared by three heavy atoms (Desiraju & Steiner, 1999).

Conventionally, the strength of a hydrogen bond can be gauged using geometrical parameters such as the hydrogen bond distance and angle. Specifically, the shorter the bond distance the stronger the interaction. Accordingly, hydrogen bond distances in the 1.2-1.5, 1.5-2.0, and 2.0-3.0 Å ranges are normally associated with very strong, strong, and weak hydrogen bonds respectively. The directional character of a hydrogen bond is manifested in its linearity (the more linear the angle, the stronger the interaction) (Desiraju & Steiner, 1999).

Close inspection of the geometrical information presented in Table 1 reveals that the poor account of correlation effects results in substantially weaker O-H…O hydrogen bonds in the HF method compared with the MP2 method. For example, relative to the MP2 method, the HF method overestimates the O6-H7…O21 hydrogen bond distance by 0.254 Å. The situation is worse for the O22-H23…O5 hydrogen bond distance for which the HF method overestimates by 0.445 Å. The MP2 method also brings these hydrogen bonds closer to linearity, although still far from 180° presumably due to the angle strain associated with the folding of the molecule. That is, the molecule is not big enough to bring the two carboxylic acid functional groups to meet fully in a linear fashion. Table 1 also shows that the strength of each of the covalent O-H bonds is overestimated as demonstrated with bond lengths that are over 0.03 Å shorter than those predicted by the MP2 method. The overestimation of covalent bonding is a characteristic of the HF method resulting from its inability to allow the population of any energetically higher than ground state molecular orbitals. In contrast, the MP2 approach allows the promotion of electron pairs from occupied to unoccupied orbitals. The population of unoccupied orbitals, including antibonding orbitals leads to a decrease in the strength of the covalent bonding (hence longer bond lengths). Moreover, the occupation of orbitals beyond the ground state electron configuration allows electrons to avoid one another, which lowers the electronic energy of the system (Cramer, 2009). The stronger covalent bonds and the lack of flexibility in the description of molecular orbital populations in the HF method (limited to the ground state molecular orbitals) results in weaker than expected noncovalent interactions as seen already in the O-

H…O hydrogen bonds in the folded conformation of azelaic acid.

The unconventional C-H…O hydrogen bonds are found to exhibit geometrical trends that mirror those of the O-H…O hydrogen bonds. For example, the C-H bond length is underestimated by 0.01 Å, and the corresponding C-H…O hydrogen bond distances are overestimated by more than 0.1 Å (Table 1). It should be noted that the weak character of the C-H…O bonds is manifested in hydrogen bond distances that are in the $2.0 - 3.0$ Å range, and angles that are far from linearity. The MP2 method brings the C-H…O bond angles a bit closer to linearity, but not by much. One distinctive feature of the C-H…O hydrogen bonds presented in Figure 2 is that they constitute what is known as a bifurcated hydrogen bond. One geometrical indicator of its strength is the planarity of the four atoms involved. The MP2 method predicts a planar bifurcated interaction while the HF method falls somewhat short in this prediction (See D(C14-H15…O5-O22 in Table 1).

In addition to geometrical indicators, vibrational frequencies help to reveal the strength of a hydrogen bond. For strong hydrogen bonds, the stretching frequencies of the covalent bonds in the hydrogen bond donors, i.e. O-H, shift to lower energies with the strength of the hydrogen bond (Scheiner, 1997). Table 2 shows that indeed the MP2 stretching frequencies are significantly smaller than the corresponding HF counterparts. It is perhaps more illustrative to consider the changes in the stretching frequencies, relative to a conformation with no intramolecular hydrogen bonds. A comparison with the optimized linear conformation shown in Figure 1 shows that the O-H stretching occurs at 4106 cm^{-1} and at 3753 cm^{-1}, at the HF and MP2 levels respectively. Formation of a hydrogen bond should weaken the covalent O-H bond and therefore shift the corresponding stretching frequency to lower wavenumbers (red shift). The larger the red shift the stronger the hydrogen bond. Accordingly, the MP2 level results in larger redshifts for both O-H stretching frequencies. For example, the O6-H7 frequency shifted to the red by 296 cm^{-1} compared with the 111 cm^{-1} shift obtained at the HF level. The smaller vibrational frequencies

upon hydrogen bond formation are consistent with the elongation of the corresponding O-H bond lengths. The O-H bond length in the linear conformation is 0.947 and 0.972 Å at the HF and MP2 levels respectively. The much longer elongation seen at the MP2 level (See Table 1 for comparison) indicates a stronger hydrogen bond interaction.

For weak C-H…O hydrogen bonds, research shows that the covalent C-H bond length actually decreases upon formation of the hydrogen bond, and the corresponding C-H stretching frequency increase (Hobza & Havlas, 2000). The C-H bond length in the linear conformation is 1.088 and 1.097 Å at the HF and MP2 levels respectively. Inspection of Table 1 confirms that there is indeed a respective reduction of the C-H bond length of 0.010 and 0.008 Å for HF and MP2. A decrease in the bond length should result in an increase of the C-H stretching frequency (a shift to the blue). A distinctive C14-H15 stretching frequency for the linear conformation occurs at 3137 cm^{-1} and at 3038 cm^{-1}, at the HF and MP2 levels respectively. Comparison with the C-H stretching frequencies listed in Table 2 confirms the shift to the blue of this vibrational mode frequency by almost the same amount in the two theoretical methods, 155 cm^{-1} (HF) and 150 cm^{-1} (MP2).

As mentioned previously, the electron density at the critical point, ρ_c, along the path of the hydrogen bond provides one measure of hydrogen bond strength. In fact, ρ_c has recently been included by IUPAC as one of the distinctive characteristics of a hydrogen bond (Arunan et al., 2011). In the case of the folded conformation of azelaic acid, Table 3 shows that the HF method consistently underestimates ρ_c, and hence the strength of the corresponding hydrogen bond relative to the MP2 level. Moreover, Table 3 makes it fairly apparent that the underestimation of bond strength is much more significant for the stronger O-H…O than for the weaker C-H…O hydrogen bonds.

Lastly, the electronic energies, including zero-point vibrational energies, of the folded conformation relative to the linear conformation

of azelaic acid are +4.46 kcal/mol and -3.67 kcal/mol at the HF and MP2 levels of theory. The positive sign for the relative energy at the HF level indicates that the folded conformation is less stable than the linear conformation, in sharp contrast to the MP2 method, which predicts the folded conformation to be preferred (at least in the gas phase).

ACKNOWLEDGEMENTS

REFERENCES

Arunan, E., Desiraju, G. R., Klein, R. A., Sadlej, J., Scheiner, S., Alkorta, I., Clary, D. C., Crabtree, R. H., Dannenberg, J. J., Hobza, P., Kjaergaard, H. G., Legon A. C., Mennucci, B., & Nesbitt, D. (2011). Definition of the hydrogen bond (IUPAC Recommendations 2011). *Pure Appl. Chem.,* 83(8), 1637–1641.

Bader, R. F. W. (1990). *Atoms in Molecules: A Quantum Theory*. Oxford Press University, New York.

Bilde, M., Svenningsson, B., Mønster, J., & Rosenørn, T. (2003). Even−Odd Alternation of Evaporation Rates and Vapor Pressures of C3−C9 Dicarboxylic Acid Aerosols. *Environmental Science & Technology*, *37*(7), 1371–1378. https://doi.org/10.1021/es0201810

Cramer, C. J. (2009). Chapter 6 and 7. In *Essentials of computational chemistry: Theories and models*. Chichester: John Wiley & Sons.

Desiraju, G. R., & Steiner, T. (1999). Chapter 1. In *The weak hydrogen bond: In structural chemistry and biology*. Oxford: Oxford University Press.

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. (2016) Gaussian 16, Revision A.03; Gaussian, Inc.: Wallingford, CT, USA.

Grimme, S., Hansen, A., Brandenburg, J. G., & Bannwarth, C. (2016). Dispersion-corrected mean-field electronic structure methods. *Chemical Reviews, 116*(9), 5105-5154. doi:10.1021/acs.chemrev.5b00533

Hobza, P., & Havlas, Z. (2000). Blue Shifting Hydrogen Bonds. *Chem Rev, 100*(11), 4253-4264.

Keith, T. A. (2013) AIMAll (Version 13.11.04), TK Gristmill Software; Overland Park, KS, USA.

Khire, S. S., Sahu, N., & Gadre, S. R. (2018). Harnessing desktop computers for ab initio calculation of vibrational IR/Raman spectra of large molecules. *Journal of Chemical Sciences*, *130*(11), 130–159. https://doi.org/10.1007/s12039-018-1568-3

National Center for Biotechnology Information Staff. (2021). PubChem Compound Summary for CID 2266, Azelaic Acid. Retrieved February 12, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Azelaic-acid.

Dennington, R., Keith, T. A., & Millam, J. M. (2016), GaussView, Version 6.1, Semichem Inc., Shawnee Mission, KS.

Scheiner, S. (1997). Chapter 5. *Hydrogen Bond: A Theoretical Perspective.* Oxford University Press; NY, USA.

Tro, J. N. (2017). *Chemistry: Structure and Properties* (2nd ed.). Pearson.