Screening Constitutional Isomers of $C_3H_2O_2$ for Thermodynamic Properties Obtained from Systematic Electron Structure Calculations

Ramkissoon C[1], Szórád JJ[2], Rágyanszki A[2], Gerlei KZ[2], Fiser B[2,3], Szőri M[2], Csizmadia IG[1,2], Knak Jensen SJ[4] and Viskolcz B[2]

1 Department of Chemistry, University of Toronto, M5S 3H6 Toronto, Ontario, Canada
2 Department of Chemical Informatics, University of Szeged, Boldogasszony sgt. 6., H-6725 Szeged, Hungary
3 Univesidad de Pais Vasco, Av. de Tolosa, 54, E-20018 Donostia, Gipuzkoa, Guipúzcoa, Spain
4 Department of Chemistry, Langelandsgade 140, Aarhus University, DK-8000 Aarhus C, Denmark

Abstract

Propiolic acid is widely employed in the synthesis and preparation of many reagents, like bis-alkynes, which has revealed cytotoxicity against B16 melanoma cancer cells. In addition, propiolic acid has antifungal and antimicrobial properties. These properties have inspired us to explore the thermodynamic properties of the isomers of propiolic acid, $C_3H_2O_2$, using electron structure calculations. In all 35 isomers were studied. The thermodynamic data can be useful in the pharmaceutical and medicinal industries.

Keywords: Bis-alkynes; Molecular isomers; Geometries; Transition state

Corresponding author: Knak Jensen SJ

✉ kemskj@chem.au.dk

Department of Chemistry, Langelandsgade 140, Aarhus University, DK-8000 Aarhus C, Denmark.

Tel: +(45) 87155926
Fax: +(45) 8619 6199

Introduction

Propiolic acid is an acetylenic compound with derivatives that may be used in different organic synthesis [1]. Acetylenic compounds can be isolated from plants, fungi and insects [2]. Some have antimicrobial and antifungal properties, which are used by organisms such as the solider beetle, *Chaudiognathus leconteri,* as a defensive mechanism against its predators [3]. There is ongoing research that focuses on the potential of acetylenic fatty acids as the forefronts in generating new topical treatments for fungal infections [4].

Propiolic acid is also used in the preparation of bis-alkynes which has revealed noticeable cytotoxicity against certain types of cancer cells such as the B16 melanoma cancer cells [5]. Computational techniques have been used to predict molecular properties of propiolic acid [6] and in the elucidation of reaction mechanism for decarboxylation of various carboxylic acids [7]. Relevant properties of propiolic acid in industrial context are found in ref. [8,9].

Traditional research in organic chemistry started with the synthesis of a given molecule. Subsequently its various properties, like thermodynamic stability, were determined experimentally. With the arrival of high-performance computers and with the associated software development one can generate all possible isomeric structures computationally via combinatorial chemistry. This allows one to construct virtual libraries of molecular isomers.

Quantum chemical molecular computations make it possible to determine the thermodynamic stability of each of these isomers even before one would attempt their synthesis in the laboratory. Various areas of non-accessible regions of chemical research would benefit from this new approach, such as drug-design and the study of molecular evolution to mention the two most obvious aspects of "molecular design". In other words this new approach can help us to study large number of molecular isomers in a variety of areas of organic chemistry.

The present study starts with a very small molecular

composition of $C_3H_2O_2$ that has only a relatively few isomers. In this case it is easier to demonstrate the various principles of this method of research.
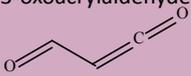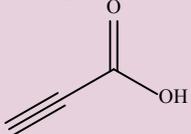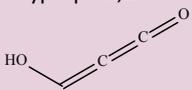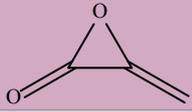
Methods

All of the isomers for $C_3H_2O_2$ with a singlet electronic state were generated using valence restrictions and geometry parameters from the MM2 molecular mechanics program. The hydrogen, oxygen and carbon atoms were considered to form bond with 1, 2 and 4 valences, respectively. The $C_3H_2O_2$ composition could occur either as a single molecule (29 cases) or as a molecular 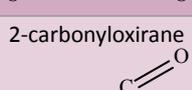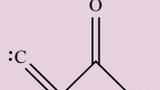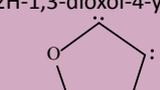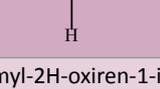complex formed from two of its fragments (6 cases). Complexes with more than two fragments were not found. Based on graph theory Molgen 5.0 program [10] was employed to generate all possible singlet state initial structures using the above mentioned restrictions. These structures were used as the primary structures to determine the local minima of the potential energy surface of $C_3H_2O_2$. Geometries were optimized at the B3LYP/6-31G(d) level of theory. The maximum optimization step size was restricted to 0.01 Bohr and the maximum number of the optimization steps were set to 300. During optimization analytical first and second derivatives were calculated in each step. The normal mode analysis was performed to secure only local minima of the multidimensional potential energy surface. After optimization, the G3MP2B3 composite method [11] was used to derive standard thermochemical properties. Subsequently, the enthalpy of formation, $\Delta_f H°$, was found using the atomization scheme. The relative Gibbs free energy values were then used to rank the thermodynamic stability of the thirty-five isomers.
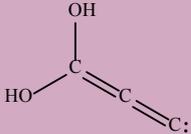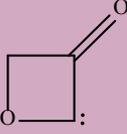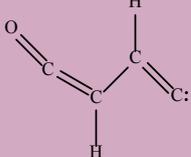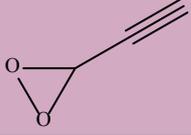
Results and Discussion

29 out of the 35 calculated molecular structures have conventional chemical bonding while the remaining 6 are bimolecular complexes consisting of two molecular fragments.

Table 1 List of the investigated 35 isomers of $C_3H_2O_2$. $\Delta_{rel}G°$ (kJ/mol) is the standard free energy relative to that of the global minimum of $[CO_2, H_2C_2]$. $S°$ (J/(mol*K)) is the standard entropy and $\Delta_f H°$ (kJ/mol) is the standard enthalpy of formation. $\Delta_{rel}G°$ and $S°$ were calculated at the G3MP2B3 level while $\Delta_f H°$ was obtained using the atomization scheme.

#	Isomer	$\Delta_{rel}G°$	$S°$	$\Delta_f H°$
1	$[CO_2,H_2C_2]$	0	352	-175.3
2	$[CH_2CO,CO]$	3.8	375	-164.8
3	3-oxoacrylaldehyde	23.4	297	-168.3
4	Propiolic acid Data for the conformer where the OH group is oriented towards the CCH moiety	81.9	298	-109.6
5	2H-oxet-2-one	96.4	284	-99.2
6	3-hydroxypropa-1,2-dien-1-one	120.9	301	-69.6
7	3-methylideneoxiran-2-one	140.5	288	-53.9
8	2-hydroxycycloprop-2-enone	164.9	290	-29.1
9	ethynyl formate	168.5	300	-22.2
10	3-hydroxypropioaldehyde	175.4	305	-13.9
11	cyclopropane-1,2-dione	198.1	305	8.8
12	2-carbonyloxirane	248.7	295	56.3
13	prop-2-yn-3-id-1-ylidyneoxidanium hydrate	249.6	361	76.8
14	2-carboxyeth-1-en-1-ylidene	256	304	66.3
15	2H-1,3-dioxol-4-yl	268.4	274	69.7
16	(S)-2-formyl-2H-oxiren-1-ium-3-ide	293.4	293	100.5
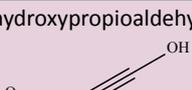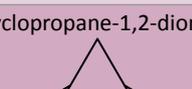
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17	3,3-dihydroxyprop-1-yn-3-ylium-1-ide	296.1	300	105.1
18	cyclopropa-1(3),2-diene-1,2-diol	302.3	291	108.8
19	2H-1λ^4-oxet-1-ylium-3-olate, 3-oxo-3,4-dihydrooxet-1-ium-2-ide	324.8	286	129.9
20	3-oxoprop-1-en-2-ylium-1-olate	333.9	310	146
21	2-(methylidyne-λ^4-oxy)ethen-1-one	368.9	300	178
22	(methylideneoxidaniumyl)ethynolate	386.3	299	195.2
23	(1R)-2-oxabicyclo[1.1.0]but-3-en-4-ol	430.5	289	236.4
24	(1r,3r)-2,4-dioxatricyclo[1.1.1.0^{1,3}]pentane	435.3	276	237.3
25	3-ethynyldioxirane	448.7	294	256.1
26	3H-1,2-dioxol-4-yl	464.9	273	265.9
27	[(3S)-3-hydroxyoxiran-2-ylidene]methylidene	470.9	297	279.2
28	3-ethenylidenedioxirane or 3-vinylidenedioxirane	478.6	296	286.5
29	$[C_2O,CH_2O]$	572.9	337	393
30	1-hydroperoxycyclopropa-1,2-diene	579.2	313	392.2
31	Complex of dioxiren-1-ium-3-ide compound with acetylene	582.2	381	415.6
32	1-[(1Z)-cycloprop-2-en-1-ylidene]dioxidan-1-ium-2-ide	613.2	294	420.5
33	3-(hydroxyoxidaniumylidene)prop-1-yn-1-ide	616.2	322	431.9
34	$[C_3,H_2O_2]$	844.6	358	670.8
35	$[C_3H_2,{}^1O_2]$	846.1	356	672
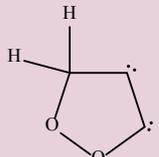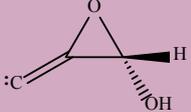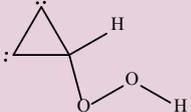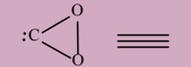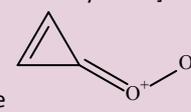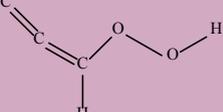
The fragments were small molecules such as CO, CO_2, H_2O_2, O_2, C_2H_2, C_2H_2O, CH_2O, C_3.

Structural comparison

Although, the structural generator software (Molgen 5.0) is expected to produce only tetravalent carbons, occasionally divalent carbene type carbon atoms have also appeared in some of the computed structures. This happened both in the open chained compounds as well as among the cyclic compounds. The structures of all of the 35 isomers are shown in **Table 1** along with their thermodynamic data. It appears that that there are many ring systems among the isomers. There are five three membered rings, eight four membered rungs and six five membered rings. The clustering of the isomers in unimolecular structures and bimolecular complexes is shown in the entropy funnel representation in **Figure 1**, which illustrates the molecular network of stable isomers associated with the potential energy hyper-surface (PEHS) that describes the $C_3H_2O_2$ empirical formula. The left-hand side of the double funnel collects all the unimolecular structures while the right hand side collects those

consisting of two fragments. Only those isomers of the network can be joined by a line that may be directly inter-converted by a chemical reaction. For example structure #4 in **Table 1** (H-CC-COOH) may undergo decarboxylation to form structure #1 ([CO_2, H_2C_2])

H-CC-COOH → [CO_2, H_2C_2]
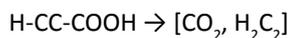
In that case structures #4 and #1, in **Figure 1**, may be inter-connected by a linear, or curvy-linear, path that has a transition state somewhere along this line.

Thermodynamic stabilities

Since the propiolic acid is a well-studied compound one might expect that it was the most stable among the isomers, but it is not. The isomer with the lowest free energy (the global minimum) turns out to be a planar complex consisting of H_2C_2 and CO_2. The complex has C_{2v} symmetry. For convenience the stability of all isomers are listed relative to the global minimum as $\Delta_{rel}G^\circ$. According to the G3MP2B3 calculations, propiolic acid exists in two conformations, differing in the orientation of the OH group relative to the CCH fragment. The conformer where the OH group is oriented away from the CCH fragment (conformer A) has a free energy which is 15 kJ/mol lower than the other isomer (conformer B). In **Table 1**, we list all the 35 isomers ranked according to $\Delta_{rel}G^\circ$. **Table 1** includes also $\Delta_f H^\circ$ and S° along with an indication of the structure.

Transition states for interconversion

Topological properties of the potential energy hyper-surface: The $C_3H_2O_2$ structure has seven atoms (n=7) implying the number of internal coordinates, 3n-6, is 15. This means that the PEHS has 15 independent variables:

$$E=f(X_1, X_2, X_3 ... X_{14}, X_{15})$$

The 35 minima are located on the PEHS, however, without explicit

knowledge of the topology of the hyper-surface it is impossible to know which pair of minima is adjacent and which ones are further separated from each other. Those that are adjacent have a transition state in between to enhance the conversion of one minimum to another. Other non-adjacent minima can only be converted through multiple conversions involving more than one transition state.

A case study for interconversion: The transition from the global minimum, [CO_2, C_2H_2], to the propionic acid isomer has been determined using the QST2 method implemented in Gausian09 [12]. The transition state was determined for both conformers of propiolic acid. It turns out that the two transition states are identical. Investigation of the transition state using the internal reaction coordinate method [12] shows that it connects the global minimum to the conformer, where the OH group is oriented towards the CCH moiety of propionic acid (conformer B). The structure of the transition state is depicted in **Figure 2**.
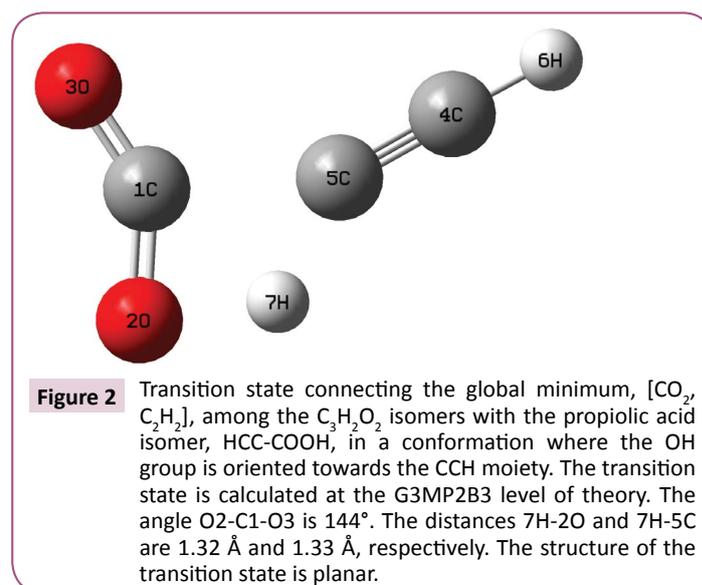

Figure 2   Transition state connecting the global minimum, [CO_2, C_2H_2], among the $C_3H_2O_2$ isomers with the propiolic acid isomer, HCC-COOH, in a conformation where the OH group is oriented towards the CCH moiety. The transition state is calculated at the G3MP2B3 level of theory. The angle O2-C1-O3 is 144°. The distances 7H-2O and 7H-5C are 1.32 Å and 1.33 Å, respectively. The structure of the transition state is planar.

Figure 1   Entropy-Funnel representation of thermodynamic properties of the 35 investigated $C_3H_2O_2$ isomers. The global minimum (#1) and the propiolic acid (#4) are indicated with an arrows.

Table 2 Barrier heights (kJ/mol) for the transition from the global minimum, [CO_2, C_2H_2], to propiolic acid calculated at various levels of theory. E_1 is the barrier from the global minimum to conformer B of propionic acid and E_2 is the barrier from conformer B to conformer A.

Level of theory	E_1	E_2
B3LYP/6-31G(d)	298	1
MP2/6-31G(d)	337	33.1
WB97XD/AUG-cc-pVDZ	297	32.7
G3MP2B3	321	32.1
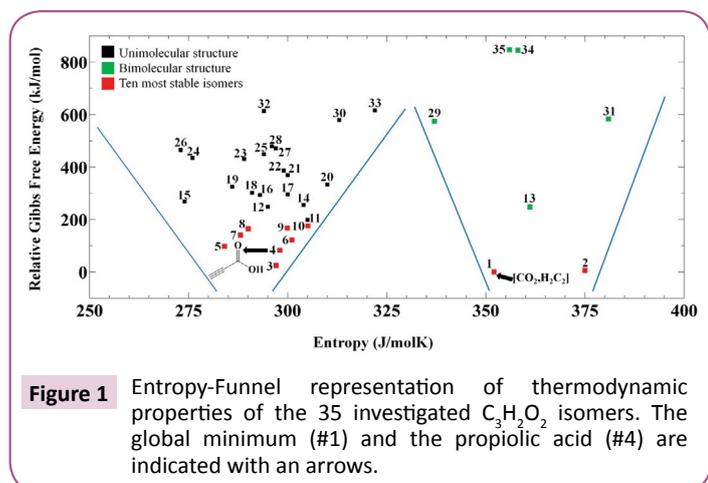
The free energy barrier for this transition at standard condition is 321 kJ/mol at the G3MP2B3 level. The barrier is so high that the reaction of CO_2 and C_2H_2 to form propionic acid will not happen - in line with observations. Calculations of the transition state using other levels of theory lead to similar estimates for the barrier height as reported in **Table 2**. Conformer B of propionic acid is connected to conformer A (which has lower free energy). A QST2 calculation leads to an estimate for the barrier height of 32 kJ/mol (G3MP2B3). Thus the transition from the global ground state to the most stable isomer of propionic acid is a two state process.

Conclusion

It was shown that new molecular structures can be predicted by molecular computations and the relative stabilities can be assessed by computing thermodynamic functions. Even though this is a small step on a long road, it is hoped that such research would be useful in designing new drugs and other desirable molecules.

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