proceedings

Proceedings

Theoretical Elucidation of the Formation of γ-Butyrolactone from Haloacetate †

Imane TEMER *, Asmaa MOSTEFAI and Ali RAHMOUNI

Laboratory of Modeling and Calculation Methods—Faculty of Sciences, University Doctor Tahar Moulay de Saida, Saida 20000, Algeria
* Correspondence: imane_temer@yahoo.fr

† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: https://ecsoc-24.sciforum.net/.

Received: date; Accepted: date; Published: date

Abstract: γ-butyrolactone is a chemical intermediate used in many organic reactions. It is also used in phytochemistry and biology for the production of growth hormones. Experimentally; the obtaining of γ-butyrolactone is done by several chemical routes; the addition of halooacétates to alkenes is an example. In this study; we will be interested on the theoretical elucidation of the addition reaction of Bromoacetate; Chloroacetate and Iodoacetate on alkene to form γ-butyrolactone. The different reactivity indices resulting from the conceptual DFT were calculated; in the first time; in order to identify the different reactional sites. A good agreement was found between the different theoretical approaches used in this study. The transition state theory approach was used; in the second time; and the different stationary states were optimized at the DFT (B3LYP) level with the basis 6-31G +(d, p). The transition states have been well located; optimized and successfully confirmed.

Keywords: bromoacetate; chloacetate; iodoacetate; γ-butyrolactone

1. Introduction

Intra or intermolecular reactions of alkenes with nucleophiles are the most common approaches to building backbones [1]. Lactones are structural building blocks in many natural products and are mainly used in agrochemicals; pharmaceuticals and organics [2]. Experimentally; the production of γ-butyrolactone is done by several chemical routes [3,4]; the addition of haloacetate to alkenes is an example We shall compare experimental work [5]; with theoretical work Figure.1.

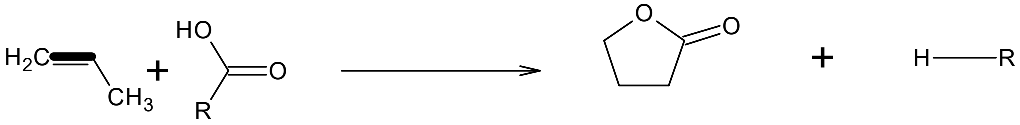


Figure 1. The reaction—γ—lactones'.

In this study; we will focus on the theoretical elucidation of the addition reaction of Bromoacetate; Chloroacetate and Iodoacetate to an alkene to form γ-butyrolactone. We have calculated at the level of the density functional theory with the pseudo potential the different global and local descriptors to target the sites of electrophilic attacks.

2. Calculation Details

The reactivity descriptors can be classified according to the degree of locality to which they correspond. Thus; the chemical potential (μ) [6]; the hardness (η) [7]; the global electrophilic index (ω) [8] and the global nucleophilicity indices N [9,10] are quantities independent of space. They take the same value at every point of the system to which they relate. They are therefore qualified as global descriptors. Alternatively; local descriptors; such as Fukui functions and local philicity are magnitudes which depend on position in space. Their values differ at each point of the system they characterize. They are therefore suitable descriptors to describe the reactivity. It is interesting to see to what extent they identify the reaction sites of alkene and haloacetates vis-à-vis electrophilic and nucleophilic attacks. To do this; the geometries of the neutral molecules were optimized at the DFT calculation level with the B3LYP functional using the pseudo potential for the iodine atom; the base LanL2dz and for the other atoms; the base 6-31G + (d, p). These geometries are held constant; for cationic and anionic systems used for the calculation of local indices of reactivity using electron populations with Mulliken population analysis (MPA).

3. Global Reactivity

In Table 1; we have given the values of the HOMO; LUMO and gap energies as well as the values of the hardness, the chemical potential and the electrophilic power of the alkene; bromoacetate (1); chloroacetate (2) and iodoacetate (3).

Table 1. Global properties of reactivity.

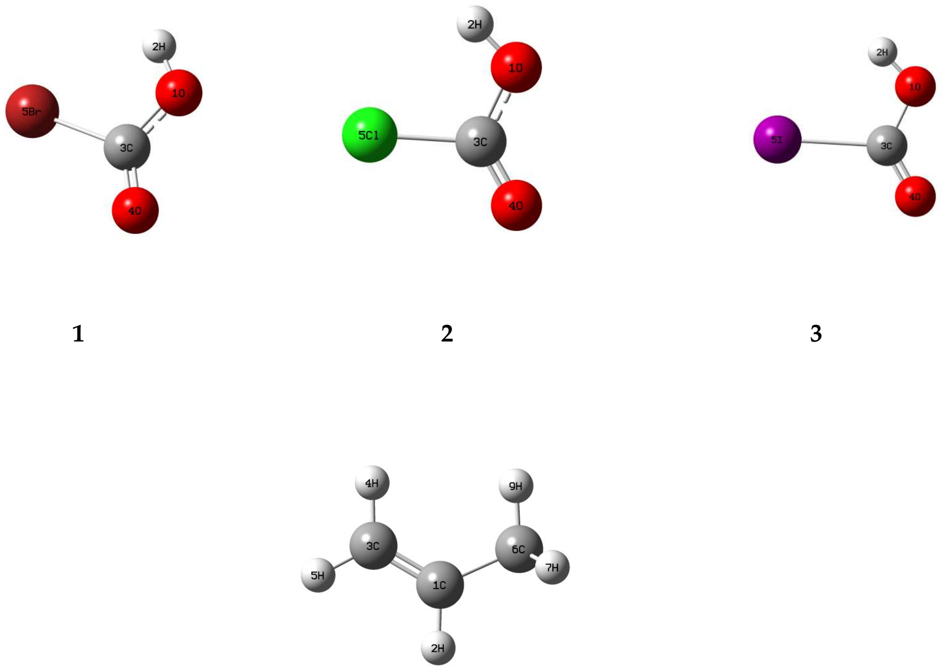
Global Descriptor	A	1	2	3
E (u.a)	−117.9228	−2760.8925	−649.3706	−200.5499
E_{HOMO} (u.a)	−0.2599	−0.3168	−0.3321	−0.2918
E_{LUMO} (u.a)	0.0024	−0.0528	−0.0333	−0.0806
GAP HOMO/LUMO	0.2623	0.2640	0.2988	0.2112
μ (ev)	−3.5020	−5.0266	−4.9694	−5.0646
η (ev)	7.1346	7.1802	8.1274	5.7446
ω (ev)	0.8595	1.7595	1.5192	2.2325
N (ev)	2.0482	0.5004	0.0843	1.1805

Table 1 show that the chemical potential μ of haloacetate 1; 2 and 3 is at an energy level higher than that of the alkene; which implies that the transfer of electrons takes place from the haloacetate to the alkene.

The nucleophilicity index of alkene is significantly higher than that of haloacetate, which means that the alkene is a nucleophile while haloacetate is an electrophile. The same conclusion can be drawn from the electrophile index values.

4. Local Reactivity

If the study of the reactivity of molecules is based on global indices deduced from electronic properties; the study of selectivity must be based on local indices. The different atoms of alkene (A); bromoacetate (1); chloroacetate (2) and iodoacetate (3) are characterized according to the numbering given in Figure 2.



1 **2** **3**

(A)

Figure 2. Optimized structure of alkene and haloacetate.

5. Net Charges on the Various Sites

In order to explain the reactivity of γ -butyrolactone, it was necessary to study the charge distribution on the different sites. Table 2 summarizes the distribution of net charges on the different sites corresponding to the alkene (A); bromoacetate (1); chloroacetate (2) and iodoacetate (3). Calculations were performed using Mulliken population analysis (MPA).

Table 2. Charge distribution of compounds A, 1, 2 and 3.

Site	MPA
compound A	
1 C	0.1225
3 C	−0.3499
6 C	−0.6169
compound 1	
1 O	−0.3439
3 C	0.3678
compound 2	
1 O	−0.3445
3 C	0.2678
compound 3	
1 O	−0.2846
3 C	0.1212

Compound A: Both C_3 and C_6 sites of the C = C bond are rich in electrons (net negative charge). However, the C_1 site is deficient in electrons (positive charge). This suggests that the C_3 and C_6 sites (the carbons of the double bond) are more favored for electrophilic attack. And the C_1 site for nucleophilic attack

Compounds 1; 2 and 3: the O_1 site is rich in electrons (net negative charge). However; the C_3 site is deficient in electrons (positive charge). This suggests that the O_1 site is more favored for an electrophilic attack. And the C_3 site for nucleophilic attack.

6. Local and Dual Reactivity Descriptors

The function of Fukui f_k^+ is a measure of the reactivity when the molecule is attacked by a nucleophilic reagent; f_k^- when the molecule is attacked by an electrophilic reagent. Thus; the most responsive site is the one with the highest Fukui function value.

From the condensed indices of Fukui; it is obviously possible to construct the condensed indices corresponding to the other local descriptors of reactivity (local electrophilic powers, dual descriptors). Note that the condensed index ω_k^+ provides information on the capacity of a site to receive electron density by nucleophilic attack. At the same time; ω_k^- provides information on the ability of a site to give up electron density by electrophilic attack.

A site with a very positive value of the dual descriptor corresponds to a site more able to receive electron density than to give up; or even more electrophilic than nucleophilic. Conversely; a site with a very negative value of the dual descriptor must correspond to a site more able to give up electron density than to receive it (more nucleophilic than electrophilic). Finally; a site with a value of the dual descriptor close to zero corresponds to a site whose capacity to receive and that to yield of the electron density are equivalent.

The function of Fukui f_k^- and ω^- provides information on the electrophilic attack. The highest value of the Fukui function is assigned to the most responsive site. Table 3 indicates the C_3 site (in compound A) and O_1 (in compounds 1, 2 and 3) are more nucleophilic and active towards electrophiles.

The function of Fukui f_k^+ and ω^+ provides information on nucleophilic attack. The highest value of the Fukui function is assigned to the most responsive site. The C_1 site (in compound A) and C_3 (in compounds 1; 2 and 3) are more nucleophilic and active with respect to nucleophiles.

The descriptors Δf_k and $\Delta\omega_k$ are capable of simultaneously explaining the electrophilia and the nucleophilia of the given atomic sites.

Table 3. The functions of Fukui f_k^- and f_k^+.

Site	f_k^+	f_k^-	ω^+	ω^-
compound A				
1 C	**−0.4136**	0.1301	**−0.3555**	0.1118
3 C	−0.1340	**0.2684**	−0.1152	**0.2307**
6 C	0.3127	−0.0153	0.2688	−0.0132
compound 1				
1 O	−0.0813	**0.1020**	−0.1430	**0.1795**
3 C	**0.3715**	0.0025	**0.6537**	0.0044
compound 2				
1 O	−0.5821	**0.1206**	−0.8843	**0.1832**
3 C	**0.8911**	−0.0176	**1.3538**	−0.0267
compound 3				
1 O	−0.0571	**0.0898**	−0.1275	**0.2005**
3 C	**0.2770**	0.0468	**0.6184**	0.1045

Table 4. Dual descriptors of reactivity in compound A.

Compound A	Δf	Δω
1 C	−0.5437	−0.4673
3 C	**−0.4024**	**−0.3459**
6 C	**0.3280**	**0.2820**

Table 4. Dual descriptors of reactivity in compound 1.

Compound 1	Δf	Δω
1 O	**−0.1833**	**−0.3225**
3 C	0.3690	0.6493

Table 4. Dual descriptors of reactivity in compound 2.

Compound 2	Δf	Δω
1 O	**−0.7027**	**−1.0675**
3 C	0.9087	1.3805

Table 4. Dual descriptors of reactivity in compound 3.

Compound 3	Δf	Δω
1 O	**−0.1469**	**−0.3280**
3 C	0.2302	0.5339

The dual descriptors are found to be particularly able to distinctly identify the strongest nucleophilic sites in haloacetates and the more electrophilic site in the alkene. Indeed, the C_1 is more nucleophilic; it will react preferentially with the electrophilic site O_1. It is interesting to note that the values of the local reactivity indices and the dual descriptors are strongly dependent on the choice of atomic bases and on the population analysis used to obtain the partial charges.

7. Prediction of the Reaction Mechanism

We have reported in Table 8 the energies of the reactants (haloacetate), the energies (E_{ts}) of the transition states TS1; TS2 and TS3 as well as the activation energy (E_a) corresponding to the formation of each reactant.

Table 8. The energies of the transition (E_{ts}), activation (E_a) states.

	$E_{reactif}$ (a.u)	E_{ts} (a.u)	$E_{product}$ (a.u)	E_a (kcal/mol)
TS_1 (1)	−2878.8203	−2878.7407	−2878.8463	49.9372
TS_2 (2)	−767.2939	−767.1946	−767.32883	62.3176
TS_3 (3)	−318.4713	−318.3920	−318.4995	**49.7599**

The energy profile corresponding to the condensation of the alkene with the haloacetate is shown schematically in Figures 3–5.

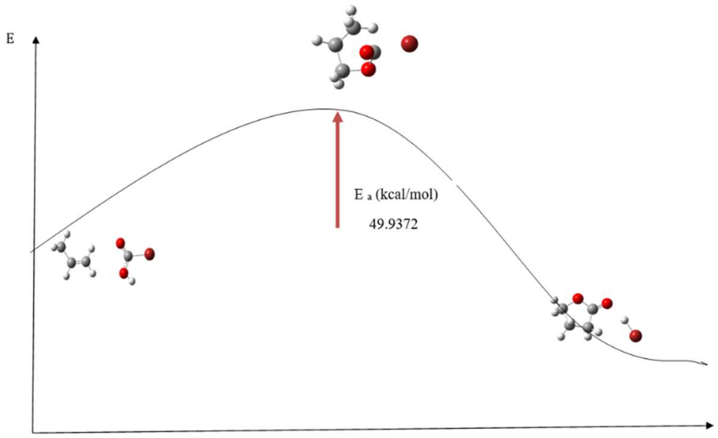


Figure 3. energy profile of bromoacetate.

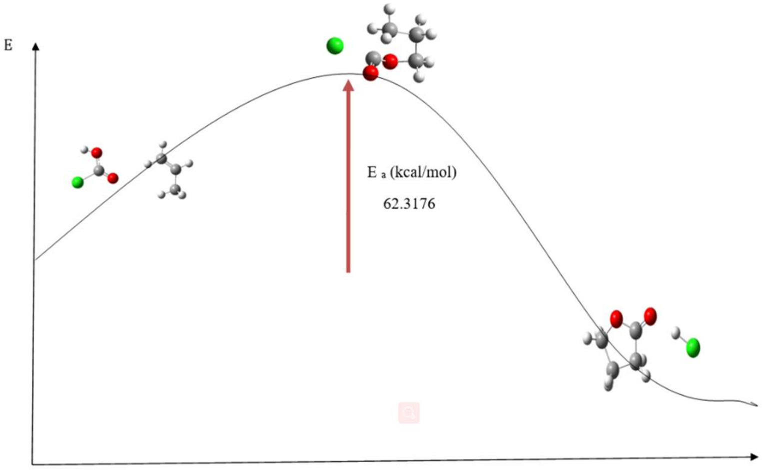


Figure 4. energy profile of chloroacetate**.**

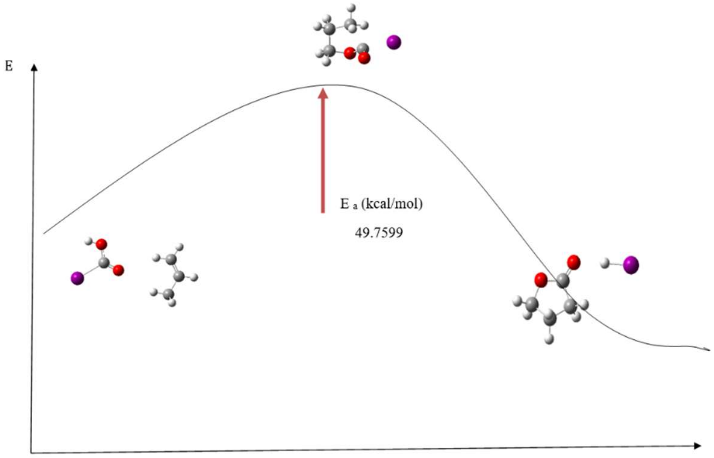


Figure 5. energy profile of iodoacetate.

The activation energy associated with the formation of gamma-butyrolactone from iodoacetate slightly higher than those associated with the formation of gamma-butyrolactone from bromoacetate and chloroacetate.

8. Conclusions

Theoretical calculation by the DFT B3LYP method of the electron density of certain atoms of the reactants; electrophilic and nucleophilic character; electrophilic and local nucleophilicity indices; the Fukui indices of the addition reaction of alkene with haloacetates; the localization of the transition states, the atomic electronic populations and the reactivity indices calculated by means of natural population (NPA) and the analysis of the Potential energy surface allowed us to conclude that:

a good match between theoretical work and experimental work
Good agreement was found between the different theoretical approaches used.
An ionic bond forms between the O_1 atom of haloacetate and the C_1 atom of the alkene.
The formation of γ-butyrolactone from haloacetate is easily done by iodoacetate.

References

1. Huang, L.; Jiang, H.; Qi, C.; Liu, X. Copper-Catalyzed Intermolecular Oxidative [3 + 2] Cycloaddition between Alkenes and Anhydrides: A New Synthetic Approach to γ-Lactones. *J. Am. Chem. Soc.* **2010**, *132*, 17652–17654, doi:10.1021/ja108073k.
2. Nefkens, G.H., Thuring, J.W.J., Beenakkers, M.F., Zwanenburg, B. Synthesis of a phthaloylglycine-derived strigol analogue and its germination stimulatory activity toward seeds of the parasitic weeds Striga hermonthica and Orobanche crenata. *J. Agric Food Chem.* **1997**, *45*, 2273–2277.
3. Ali, M.T.M. SYNTHESIS OF (-)-GEISSMAN WAISS LACTONE, cis γ-BUTYROLACTONE DERIVATIVES AND γ-PEPTIDES. Ph.D. Thesis, Universität Regensburg, Regensburg, Germany, 2011.
4. Semak, V.; Boháč, A.; Sališová, M.; Addová, G.; Danko, P. Preparation of α-methyl-γ-butyrolactone: Mechanism of its formation and utilization in 2-methyl-1-tetralone synthesis. *Chem. Pap.* **2008**, *62*, 275–280, doi:10.2478/s11696-008-0023-1.
5. Maejima, S.; Yamaguchi, E.; Itoh, A. trans-Diastereoselective Syntheses of γ-Lactones by Visible Light-Iodine-Mediated Carboesterification of Alkenes. *ACS Omega* **2019**, *4*, 4856–4870, doi:10.1021/acsomega.9b00333.
6. Parr, R.G.; Pearson, R.G. Absolute hardness: Companion parameter to absolute electronegativity. *J. Am. Chem. Soc.* **1983**, *105*, 7512–7516, doi:10.1021/ja00364a005.
7. Maynard, A.T.; Huang, M.; Rice, W.G.; Covell, D.G. Reactivity of the HIV-1 nucleocapsid protein p7 zinc finger domains from the perspective of density-functional theory. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 11578–11583, doi:10.1073/pnas.95.20.11578.
8. Domingo, L.R.; Chamorro, E.; PérezP. Understanding the Reactivity of Captodative Ethylenes in Polar Cycloaddition Reactions. A Theoretical Study. *J. Org. Chem.* **2008**, *73*, 4615–4624, doi:10.1021/jo800572a.
9. Domingo, L.R.; Pérez, P. The nucleophilicity N index in organic chemistry. *Org. Biomol. Chem.* **2011**, *9*, 7168–7175, doi:10.1039/c1ob05856h.
10. Parr, R.G.; Szentpály, L.V.; Liu, S. Electrophilicity Index. *J. Am. Chem. Soc.* **1999**, *121*, 1922–1924, doi:10.1021/ja983494x.