



Research Article

ISSN : 0975-7384  
CODEN(USA) : JCPRC5

**Computational and Chemometrics study of molecular descriptors for butene derivatives by Density functional theory (DFT).**

N. Surendra Babu and Isaac Onoka

Department of Chemistry, College of Natural and Mathematical Sciences, The University of Dodoma, Post Box No: 259, Dodoma, Tanzania

---

**ABSTRACT**

*In this work we have been calculated global and local DFT reactivity descriptors for butane derivatives at B3LYP/6-311++G (d, p) level. Global reactivity descriptors such as ionization energy (IP), electron affinity (EA) molecular hardness ( $\eta$ ) and electrophilicity ( $\omega$ ), were calculated to evaluate the for butane derivatives reactivity in gas phase. The chemometric methods PCA and HCA were employed to find the subset of variables that could correctly classify the compounds according to their reactivity. From the PCA and HCA results in this work, a classification model was built with the aim to be used in the search for butene derivatives for the reactivity.*

**Key words:** Butene derivatives, Density functional Theory, molecular descriptors and Principal component analysis (PCA) and hierarchical cluster analysis (HCA).

---

**INTRODUCTION**

1-butene is a linear alpha olefin (alkene), produced either by separation from crude C4 refinery streams or from the reaction of ethylene. It is distilled to give a very high purity product. 1-butene is used in the manufacture of a variety of other chemical products. It fills an important role in the production of materials such as linear low density polyethylene (LLDPE). The co-polymerisation of ethylene and 1-butene produces a form of polyethylene that is more flexible and more resilient. 1-butene can also help to create a more versatile range of polypropylene resins. It is also used in the production of polybutene, butylene oxide and in the C4 solvents secondary butyl alcohol (SBA) and methyl ethyl ketone (MEK).

Density functional theory based descriptors have found immense usefulness in the prediction of reactivity of atoms and molecules as well as site selectivity [1–5]. The resourcefulness of density functional descriptors in the development of QSAR has been recently reviewed by Chattaraj et al [6]. Chemical hardness ( $\eta$ ), chemical potential ( $\mu$ ), electrophilicity index ( $\omega$ ) and softness ( $s$ ) are known as global reactivity descriptors. Recently Parr et al.[7] have defined a new descriptor to quantify the global electrophilic power of the molecule as electrophilicity index ( $\omega$ ), which defines a quantitative classification of the global electrophilic nature of a molecule within a relative scale. The earlier works of Maynard et al.[8] have formed the strong foundation for the electrophilicity index ( $\omega$ ), which provided the direct relationship between the rates of reaction and the ability to identify the function or capacity of an electrophile and the electrophilic power of the inhibitors.

Chemometrics refers to the application of statistical and mathematical methods, in particular multivariate methods, to handle chemical or process data. The need for chemometrics methods originates from the massive amounts of

data produced by modern measuring devices [9, 10]. Chemometrics tends to deal with data tables or matrices consisting of several variables (columns of tables or matrices) and measurement targets (rows or tables or matrices) as a whole rather than as single variables or means or variations of single variables [11]. This multivariate approach enables finding the so-called latent variables or information of interrelated variables in the original data matrix which can then be extracted. The latent variable models are based on the assumption that the original data base dimensionality is not a full rank [12]. The new latent variables are projections of the original variables on multivariate space. Thus, even the 100 dimensional variable spaces can be reduced into a subspace consisting of a few latent variables that describes underlying phenomena [13] such that the originally 100 dimensional space can be visualized. There are several advantages of using multivariate methods over univariate techniques [14] such as robust modeling, noise removal, handling of interacting variables or overlapping spectral profiles, outlier or fault detection [12,14], variable reduction and understanding the reasons for similarity or dissimilarity of measurements (interpretation plus causality).

The present work reports the results of a systematic theoretical examination of butene derivatives and isomers calculate more representative descriptors. Furthermore, the multivariate methods, such as a principal component analysis (PCA) and hierarchical cluster analysis (HCA), have been employed with the aim of selecting the variables responsible for reactivity and to describe properly the relationship between the calculated descriptors of title compound derivatives.

## EXPERIMENTAL SECTION

### Quantum Chemical Calculation

All of the molecular structures were constructed by using ChemDraw Ultra 8.0. For every molecule, structure was suitably changed considering its structural features copied to Chem3D Ultra 8.0 to create 3-D model, the model was subjected to energy minimization using (Dewar et al. 1985). The geometries of all compounds investigated were completely optimized with the GAUSSIAN 09W program [15], employing the Becke3LYP functional [16–18] of the density functional theory [19, 20] (DFT) with the polarized triple zeta split valence 6–311++G (d,p) basis set. Moreover, the frequency calculations were performed to verify the optimized structures to be at an energy minimum.

### Statistical Analysis

In this study, the correlation between the molecular properties calculated and the stability and reactivity studied was done by using the pattern recognition methods (PCA and HCA). This statistical method has been applied by using the statistical software Minitab 15 and kyPlot package programs.

## RESULTS AND DISCUSSION

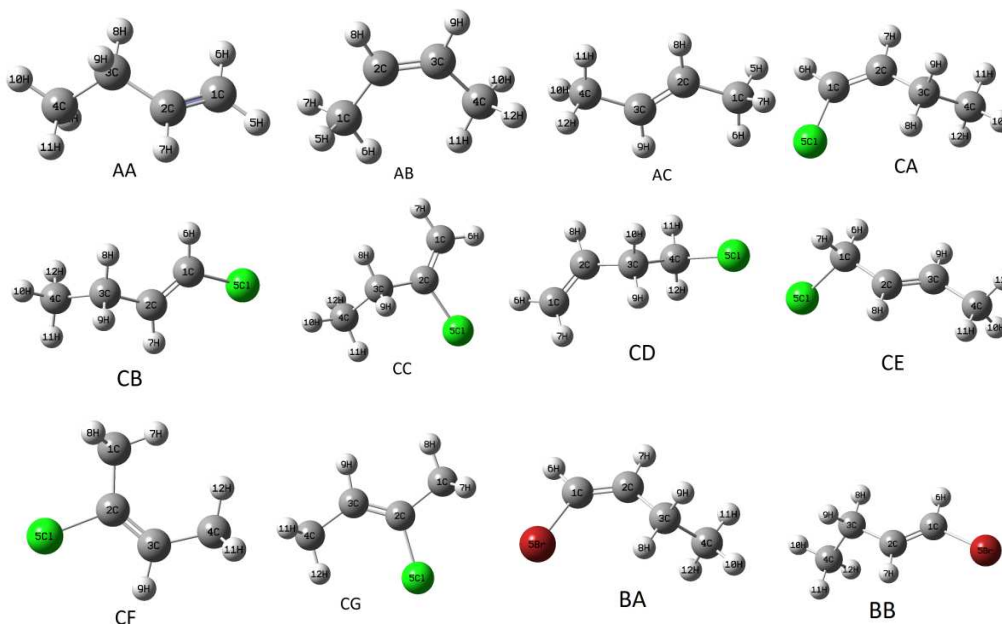
### Relative stability

The structures correspond to butene molecules labeled as code shown in Table 1 and these differ for chlorine, bromine, both chlorine and bromine, nitrogen and oxygen atoms and hydroxy group at the different position in butane molecule.

The optimized geometrics are shown in Figure 1 in gas phase. The absolute electronic energies and dipole moments are presented in Table 2, in gas phase, at DFT levels of theory in conjunction with 6-311++G (d,p) basis set.

Table 1. The energies of butane derivates (in a.u) and dipole moments ( $\mu$ , in Debye units) at DFT/6-311++G (d,p) level in gas phase

S.No	Name	code	$\mu$	Energy
1	1-Butene	AA	0.4174	-157.26971212
2	cis-2-butene	AB	0.2572	-157.27264225
3	trans-2-butene	AC	0.0000	-157.27461287
4	cis-1-chloro-1-butene	CA	1.7881	-616.89416900
5	trans-1-chloro-1-butene	CB	2.1616	-616.89393023
6	2-chloro-1-butene	CC	1.8149	-616.89619493
7	4-chloro-1-butene	CD	2.1428	-616.89316452
8	1-chloro-2-butene	CE	2.6973	-616.89790700
9	cis-2-chloro-2-butene	CF	2.2381	-616.89910745
10	trans-2-chloro-2-butene	CG	1.8246	-616.90122407
11	cis-1-bromo-1-butene	BA	1.8217	-2730.81463432
12	trans-1-bromo-1-butene	BB	2.1878	-2730.81452679
13	2-bromo-1-butene	BC	1.8388	-2730.81577995
14	4-bromo-1-butene	BD	2.1572	-2730.81464954
15	1-bromo-2-butene	BE	2.7225	-2728.36696084
16	cis-2-bromo-2-butene	BF	2.2945	-2730.81888646
17	trans-2-bromo-2-butene	BG	1.8784	-2730.82083354
18	(Z)-1-bromo-4-chlorobut-2-ene	EA	3.2469	-3190.43758269
19	(E)-1-bromo-4-chlorobut-2-ene	EB	0.4613	-3190.43798246
20	(Z)-1-bromo-2-chlorobut-2-ene	EC	3.0214	-3190.44229628
21	trans-2-butenedinitrile	NA	0.0000	-263.14432269
22	cis-2-butene-1,4 diol	DA	4.2045	-307.64207533
23	trans-2-butene-1,4 diol	DB	2.6883	-307.74839007
24	cis-2-butenenitrile	NB	4.3742	-210.21547790
25	trans-2-butenenitrile	NC	4.8666	-210.21532459
26	3-butenenitrile	ND	4.0501	-210.20601765
27	cis-2-buten-1-ol	OA	1.8941	-232.50809714
28	trans-2-buten-1-ol	OB	2.2780	-232.51306515
29	3-buten-1-ol	OC	1.7459	-232.50766915
30	3-buten-2-ol	OD	1.8638	-232.51029372
31	3-buten-2-one	OE	2.9337	-231.30717297
32	1-buten-3-yne	YA	0.4254	-154.78337549



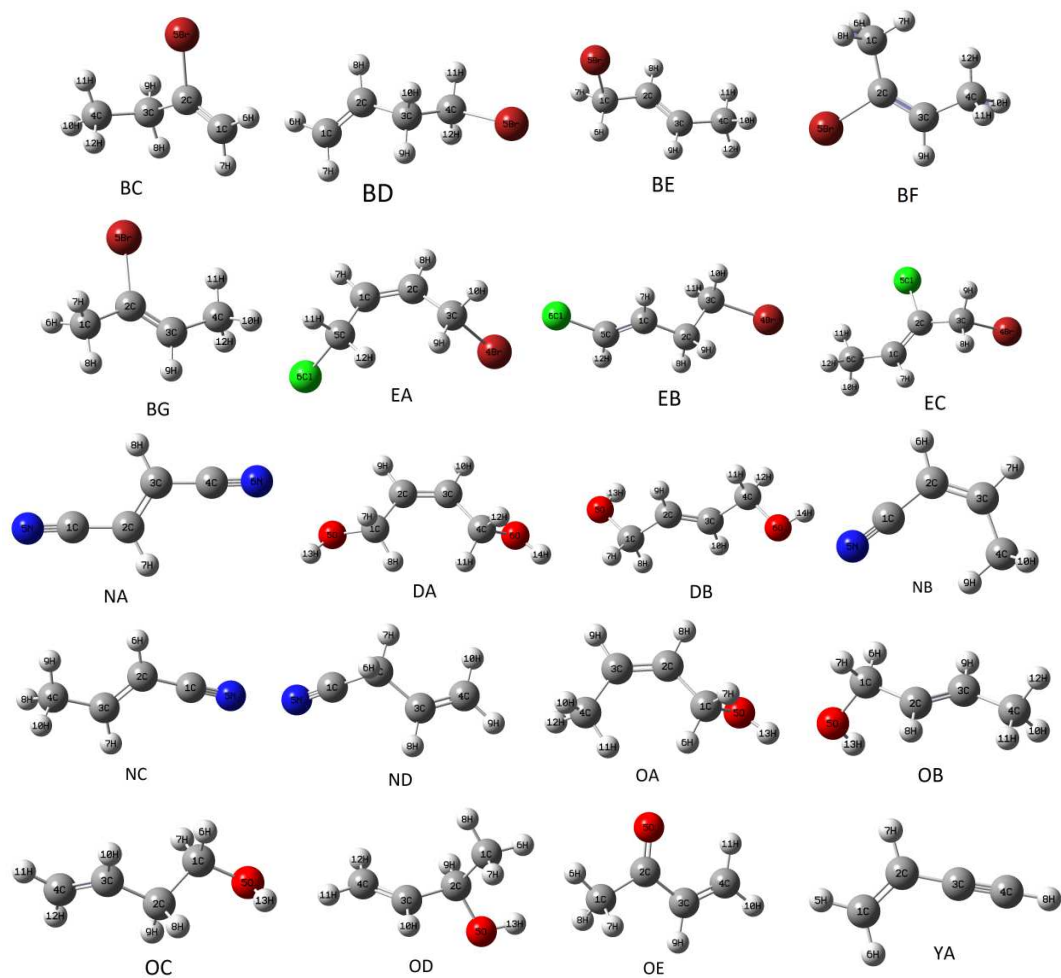


Figure:1. The optimized structures of butane derivates in gas phase at DFT/B3LYP/6-311++G (d,p) level

Table:1. The energies of butane derivates (in a.u) and dipole moments ( $\mu$ , in Debye units) at DFT/6-311++G(d,p) level in gas phase

S.No	Name	code	$\mu$	Energy
1	1-Butene	AA	0.4174	-157.26971212
2	cis-2-butene	AB	0.2572	-157.27264225
3	trans-2-butene	AC	0.0000	-157.27461287
4	cis-1-chloro-1-butene	CA	1.7881	-616.89416900
5	trans-1-chloro-1-butene	CB	2.1616	-616.89393023
6	2-chloro-1-butene	CC	1.8149	-616.89619493
7	4-chloro-1-butene	CD	2.1428	-616.89316452
8	1-chloro-2-butene	CE	2.6973	-616.89790700
9	cis-2-chloro-2-butene	CF	2.2381	-616.89910745
10	trans-2-chloro-2-butene	CG	1.8246	-616.90122407
11	cis-1-bromo-1-butene	BA	1.8217	-2730.81463432
12	trans-1-bromo-1-butene	BB	2.1878	-2730.81452679
13	2-bromo-1-butene	BC	1.8388	-2730.81577995
14	4-bromo-1-butene	BD	2.1572	-2730.81464954
15	1-bromo-2-butene	BE	2.7225	-2728.36696084
16	cis-2-bromo-2-butene	BF	2.2945	-2730.81888646
17	trans-2-bromo-2-butene	BG	1.8784	-2730.82083354
18	(Z)-1-bromo-4-chlorobut-2-ene	EA	3.2469	-3190.43758269
19	(E)-1-bromo-4-chlorobut-2-ene	EB	0.4613	-3190.43798246
20	(Z)-1-bromo-2-chlorobut-2-ene	EC	3.0214	-3190.44229628
21	trans-2-butenedinitrile	NA	0.0000	-263.14432269
22	cis-2-butene-1,4 diol	DA	4.2045	-307.64207533
23	trans-2-butene-1,4 diol	DB	2.6883	-307.74839007
24	cis-2-butenenitrile	NB	4.3742	-210.21547790
25	trans-2-butenenitrile	NC	4.8666	-210.21532459
26	3-butenenitrile	ND	4.0501	-210.20601765
27	cis-2-buten-1-ol	OA	1.8941	-232.50809714
28	trans-2-buten-1-ol	OB	2.2780	-232.51306515
29	3-buten-1-ol	OC	1.7459	-232.50766915
30	3-buten-2-ol	OD	1.8638	-232.51029372
31	3-buten-2-one	OE	2.9337	-231.30717297
32	1-buten-3-yne	YA	0.4254	-154.78337549

The results show that the chloro and bromo derivates of butane molecules are most unstable. The order of stability of derivates was found to be butane > nitrogen  $\approx$  oxygen  $\approx$  hydroxyl group > chloro > bromo > chloro and bromo. Figure 2 shows the effect of substituent's on the stability of butane. From the radar graph the dipole moments shows the nitrogen, hydroxyl group and the both chloro -bromo derivates of butanes' have high values comparison of other derivates.

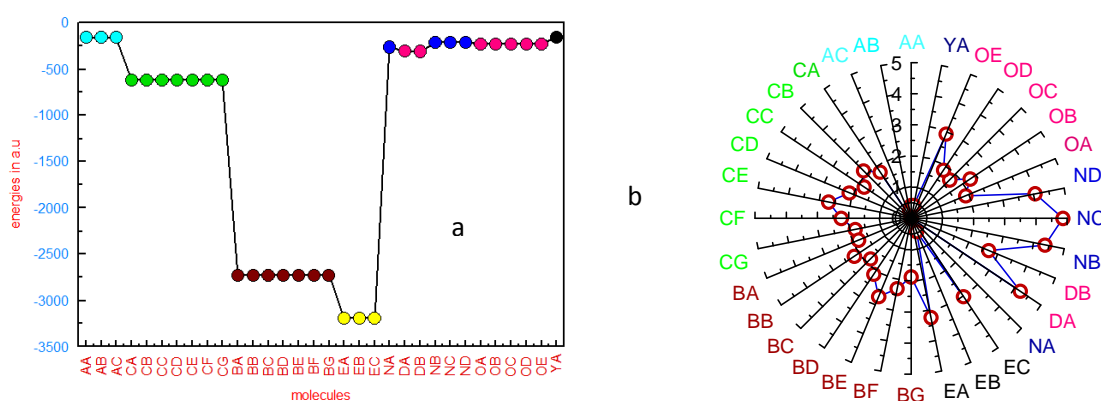


Figure: 2. the plots of (a) energies vs molecules and the radar graph (b) of dipole moments for butane derivates in gas phase

**Global and local reactivity descriptors**

According to, the Koopmans' theorem [21] for closed-shell molecules, ionization potential (I) and electron affinity (A) can be expressed as follows in terms of E(HOMO) and E(LUMO) the highest occupied molecular orbital energy, and the lowest unoccupied molecular orbital energy, respectively:

$$IP = -E_{HOMO} \quad \text{and} \quad EA = -E_{LUMO} \quad (1)$$

When the values of I and A are known, one can determine through the following expressions [22] the values of the absolute electron negativity ( $\chi$ ), the absolute hardness ( $\eta$ ), the chemical potential ( $\mu$ ) and the softness S[23] (the inverse of the hardness):

$$\chi = \frac{I+A}{2}; \quad \eta = \frac{I-A}{2}; \quad \mu = -\frac{(I+A)}{2} \quad \text{and} \quad s = \frac{1}{\eta} \quad (2)$$

The electrophilicity is a descriptor of reactivity that allows a quantitative classification of the global electrophilic nature of a molecule within a relative scale. Parr have proposed electrophilicity index as a measure of energy lowering due to maximal electron flow between donor and acceptor and defined electrophilicity index ( $\omega$ ) as follows[24].

$$\omega = \frac{\mu^2}{2\eta} \quad (3)$$

According to the definition, this index measures the propensity of chemical species to accept electrons. A good, more reactive, nucleophile is characterized by lower value of  $\mu$ ,  $\omega$ , and conversely a good electrophile is characterized by a high value of  $\mu$ ,  $\omega$ . This new reactivity index measures the stabilization in energy when the system acquires an additional electronic charge  $\Delta N_{\max}$  from the environment [25].

$$\Delta N_{\max} = -\frac{\mu}{\eta} \quad (4)$$

The maximum charge transfer  $\Delta N_{\max}$  towards the electrophile was evaluated using Eq. (4). Thus, while the quantity defined by Eq. (3) describes the propensity of the system to acquire additional electronic charge from the environment; the quantity defined in Eq. (4) describes the charge capacity of the molecule.

Very recently, Ayers and co-workers [26, 27] have proposed two new reactivity indices to quantify nucleophilic and electrophilic capabilities of a leaving group, nucleofugality ( $\Delta E_n$ ) and electrofugality ( $\Delta E_e$ ), defined as follows,

$$\Delta E_n = EA + \omega = \frac{(\mu + \eta)^2}{2\eta} \quad \text{and} \quad \Delta E_e = IP + \omega = \frac{(\mu - \eta)^2}{2\eta} \quad (5)$$

The global descriptors, chemical potential, chemical, hardness and chemical softness for all studied isomers are given in Table 3. Ionization energy is a fundamental descriptor of the chemical reactivity of atoms and molecules. High ionization energy indicates high stability and chemical inertness and small ionization energy indicates high reactivity of the atoms and molecules. Absolute hardness and softness are important properties to measure the molecular stability and reactivity. It is apparent that the chemical hardness fundamentally signifies the resistance towards the deformation or polarization of the electron cloud of the atoms, ions or molecules under small perturbation of chemical reaction.

**Chemometric analysis**

Principal component analysis (PCA) Principal component analysis (PCA), is a linear projection method and used for reduction of dimensionality and multivariate data compression. The idea of PCA dates back in 19th century and was named by Hotelling in 1933 [28, 29]. At that time, mathematicians explored multivariate data by fitting it onto lines

and planes [28]. Today, PCA is one of the vast utilized multivariate methods since its wide applicability for multivariate problems. PCA is deployed for data compression [30] and data exploring within different fields of science. PCA is also used for checking groupings of the X data, as well as grouping among the Y data matrix [31, 32]. In process monitoring, PCA is used to detect trends, to find a correlation structure of variables and, in particular, to examine the changes in variable correlations [32, 33]. It should be noted that PCA is feasible for variable reduction if variables are correlated and thus contain a similar variance.

**Clustering Methods** Clustering is a data analysis technique that, when applied to a set of heterogeneous items, identifies homogeneous subgroups as defined by a given model or measure of similarity. Of the many uses of clustering, a prime motivation for the increasing interest in clustering methods is their use in the selection and design of combinatorial libraries of chemical structures pertinent to pharmaceutical discovery. Clustering methodology has been developed and used in a variety of areas including archaeology, astronomy, biology, computer science, electronics, engineering, information science, and medicine.

The overall process of clustering involves the following steps: 1. Generate appropriate descriptors for each compound in the data set. 2. Select an appropriate similarity measure. 3. Use an appropriate clustering method to cluster the data set. 4. Analyze the results. To address this problem, many numerical clustering techniques have been developed, and the techniques themselves have been classified. For our purposes the methods considered belong to one of the following types. (a) Hierarchical techniques in which the elements or objects are clustered to form new representative objects, with the process being repeated at different levels to produce a tree structure, the dendrogram. (b) Methods employing optimization of the partitioning between clusters using some type of iterative algorithm, until some predefined minimum change in the groups is produced. (c) Fuzzy cluster analysis in which objects are assigned a membership function indicating their degree of belonging to a particular group or set. In this study, multivariate chemometric techniques have been applied in evaluating grouping operations in butene derivatives.

From PCA results, we can observe that the first three principal components (PC1, PC2 and PC3) describe 99.89% of the overall variance as follows: PC1 = 80.69%, PC2 = 17.74% and PC3 = 1.46%. Since almost all of the variance is explained by the first two PCs, their score plot is a reliable representation of the spatial distribution of the points for the data set studied. The most informative score plot is presented in Figure 3 (PC1 versus PC2) and we can see that PC1 alone is responsible for the separation between more active and less active molecules.

Looking at Figure 3, we can see that the studied thirty two molecules were separated into four groups based on PC1 and PC2. The first group consisting of ND, NA, NC, NB, DB, EB, EA, BE, EC, YA, and OE molecules belong to  $PCA > 1$  and remaining molecules  $PCA < 1$ . The principal component 1 ( $PC1 > 0$ ) molecules are the more active and  $PC1 < 0$  for the less active molecules. The same results follow in the case of global reactivity trend based on  $\omega$ .

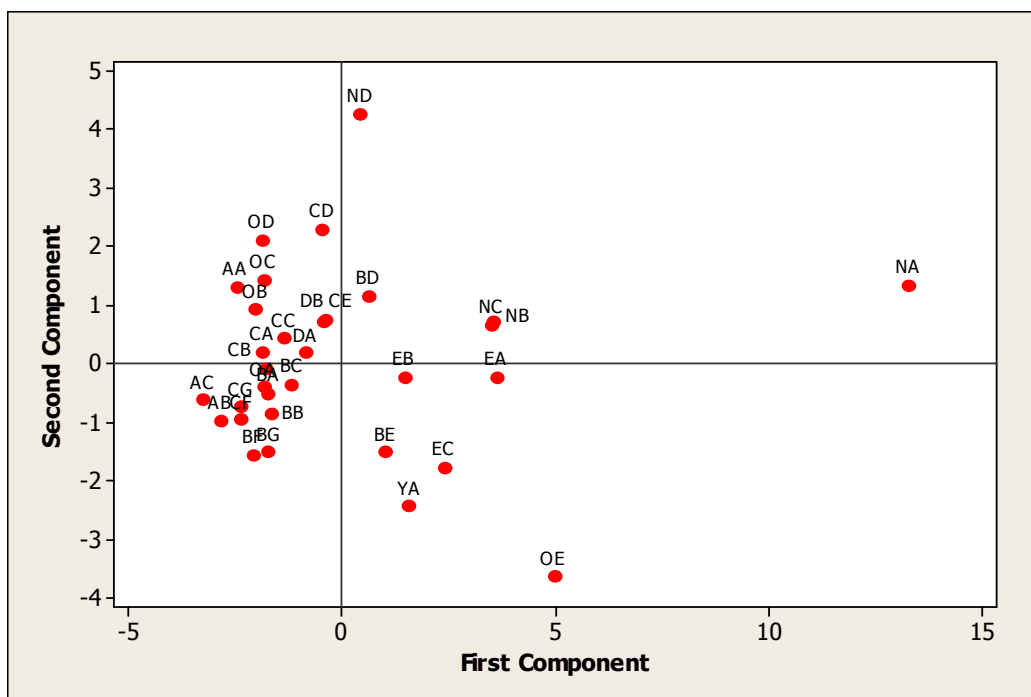


Figure: 3. Score plot for the butane derivatives

The loading vectors for the first two principal components (PC1 and PC2) are displayed in Figure 4. According to loading plot, PC1 can be expressed through the following equation.

$$\text{PC1} = -0.7933[\text{HOMO}] - 0.9947[\text{LUMO}] + 0.7933 [\text{IP}] + 0.9947[\text{EA}] + 0.9760[\chi] - 0.7218[\eta] - 0.9760[\mu] + 0.7538 [s] + 0.9963[\omega] + 0.9920 [\Delta N_{\text{max}}] + 0.9008[\Delta E_n] + 0.9775 [\Delta E_e] + 0.7218[\Delta E_g \text{ gap}] \quad (6)$$

From equation (6) we can see that more active tautomers compounds ( $\text{PC1} > 0$ ) can be obtained when we have higher IP, EA,  $\chi$ , s,  $\omega$ ,  $\Delta N_{\text{max}}$ ,  $E_n$ ,  $E_e$ , values (notice that A,  $\chi$ , s,  $\omega$ ,  $\Delta N_{\text{max}}$ ,  $E_n$  and  $E_e$ , have positive coefficients in PC1 equation) combined with negative  $\eta$  values for the less active molecules. In this way, some important features on the more active molecules can be observed:



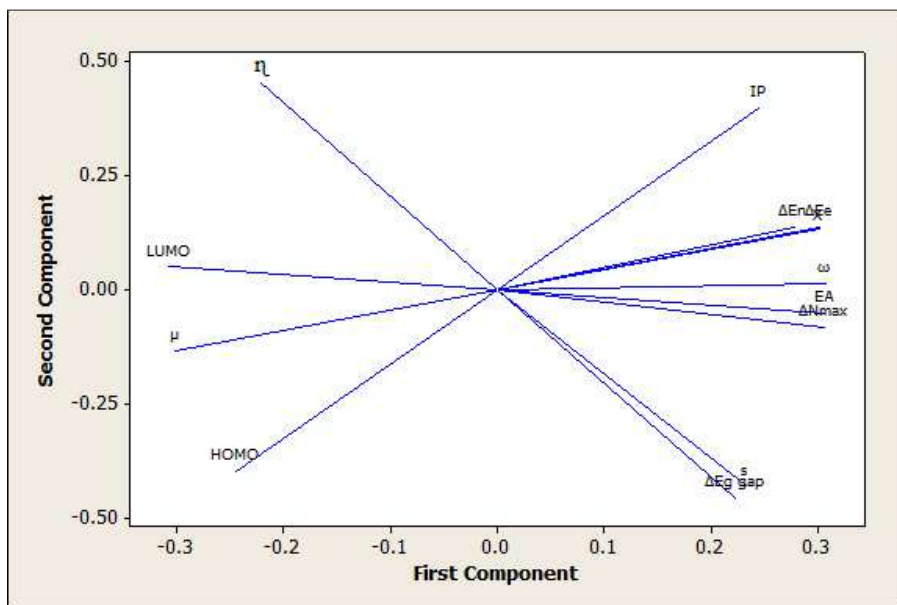


Figure 4. Loading plot for the thirteen variables responsible for the classification of the butane derivatives studied: I = ionization potential; A = electron affinity;  $\chi$  = electron negativity;  $\eta$  = hardness;  $s$  = softness;  $\mu$  = chemical potential;  $\omega$  = electrophilicity;  $\Delta N_{max}$  = an additional electronic charge from environment;  $\Delta E_n$  and  $\Delta E_e$  = nucleophilic and electrophilic capabilities of a leaving group; all in electron volts units

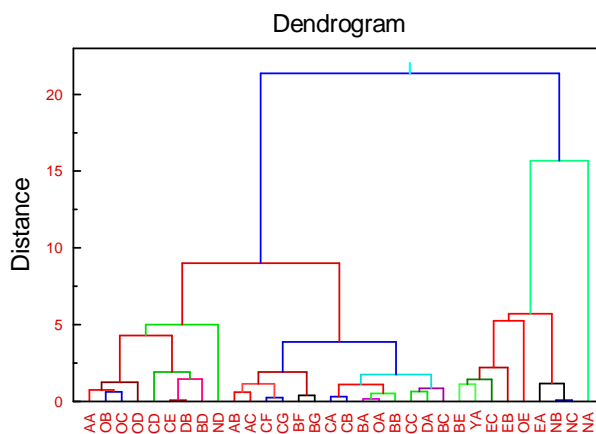


Figure 5. Dendrogram obtained for the thirty two butane derivatives

**Hierarchical Cluster Analysis (HCA)**

Figure 5 shows HCA analysis of the present study. The horizontal lines represent the compounds and the vertical lines the similarity values between pairs of compounds, a compound and a group of compounds and among groups of compounds. The number of clusters, similarity levels, distance levels, clusters of joined and number of observes in the new cluster are presented in the Table. 3.

Table 3. the number of clusters, similarity levels, distance levels, clusters of joined and number of observes in the new cluster

Step	Number of clusters	Similarity level	Distance level	Clusters joined		Number of obs in new cluster
1	31	99.7159	0.03277	NB	NC	2
2	30	99.6226	0.04353	CE	DB	2
3	29	99.4093	0.06813	BA	OA	2
4	28	99.2637	0.08494	CF	CG	2
5	27	99.0835	0.10572	CA	CB	2
6	26	98.8708	0.13025	BA	BB	3
7	25	98.7419	0.14512	CA	BA	5
8	24	97.9860	0.23231	BF	BG	2
9	23	97.7804	0.25602	CF	BF	4
10	22	97.6648	0.26936	AB	AC	2
11	21	97.6483	0.27126	OC	OD	2
12	20	97.5476	0.28288	CA	OB	6
13	19	97.4886	0.28968	CA	OC	8
14	18	97.4748	0.29128	AA	CA	9
15	17	97.4737	0.29140	AA	CF	13
16	16	97.3812	0.30207	CC	BC	2
17	15	97.0979	0.33476	AA	AB	15
18	14	97.0676	0.33825	EA	NB	3
19	13	97.0546	0.33974	CC	DA	3
20	12	96.6478	0.38667	AA	CC	18
21	11	96.5120	0.40233	15	YA	2
22	10	96.4484	0.40967	AA	CE	20
23	9	94.6793	0.61374	AA	CD	21
24	8	94.5440	0.62934	BD	EB	2
25	7	94.0696	0.68406	BD	BE	4
26	6	93.9773	0.69471	BD	EC	5
27	5	93.5916	0.73920	AA	BD	26
28	4	89.7598	1.18118	AA	ND	27
29	3	89.5417	1.20634	AA	EA	30
30	2	88.8939	1.28106	AA	OE	31
31	1	41.0702	6.79743	AA	NA	32

From Figure 5, we can see that the HCA results are very similar to those obtained with the PCA analysis, i.e. the compounds studied were grouped into four groups.

### CONCLUSION

The derivatives of the butane were theoretically investigated with the density functional theory employing B3LYP method with the 6-311+G (d,p) basis set. The order of stability of derivatives was found to be butane > nitrogen  $\approx$  oxygen  $\approx$  hydroxyl group > chloro > bromo > chloro and bromo with respect to absolute energies. From PCA results, we can see that PC1 alone is responsible for the separation between more active and less active molecules. PC1 > 0 is more reactive compounds, and PC1 < 0 for the less reactive molecules respectively. From the HCA results are very similar to those obtained with the PCA analysis.

### Acknowledgement

The authors thankful to Dr. P.V.Kanaka Rao, Associate professor, department of Physics, College of Natural and Mathematical Sciences, The University of Dodoma, to help for the chemometrics analysis.

### REFERENCES

- [1] M Karelson; VS Lobanov; AR Katritzky, *Chem. Rev.*, **1996**, 96, 1027.
- [2] G Parr, *Annu. Rev. Phys. Chem.*, **1983**, 34, 631.
- [3] RG Parr; W Yang, *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, UK, **1989**.
- [4] HJ Chermette, *Comput. Chem.*, **1999**, 20, 129.
- [5] P Geerlings; F De Proft; W Langenaeker, *Chem. Rev.*, **2003**, 103, 1793.

- [6] PK Chattaraj; S Nath; B Maiti, Reactivity Descriptors. In Computational Medicinal Chemistry for Drug Discovery; Eds.; MarcelDekker: New York, **2003**, pp 295–322, Chapter 11.
- [7] RG Parr; LV Szentpaly; SJ Liu, *Am. Chem. Soc.*, **1999**, 121, 1922.
- [8] AT Maynard; M Huang; WG Rice; DG Cove, *Proc. Natl. Acad. Sci. U.S.A.* **1998**, 95, 11578.
- [9] P Geladi; K Esbensen, *J.Chemometr.*, **1990**, 4, 337.
- [10] K Esbensen; P Geladi, *J. Chemometr.*, **1990**, 4, 389.
- [11] J Workman, *Chemometr Intell Lab.*, **2002**, 60, 13.
- [12] T Kourti, *Crit Rev Anal Chem.*, **2006**, 36, 257.
- [13] R Bro, *Anal Chim Acta.*, **2003**, 500, 185.
- [14] T Kourti; P Nomikos ; M JF, *J. Proc Cont.*, **1995**, 5, 277.
- [15] MJ Frisch; GW Trucks; HB Schlegel; PMW Gill; BG Johnson; MA Robb et al., GAUSSIAN 09, Revision, Gaussian, Inc., Wallingford CT, **2009**.
- [16] AD Becke, *Phys. Rev.*, **1988**, A38, 3098.
- [17] AD Becke., *J. Chem. Phys.*, **1993**, 98, 5648.
- [18] C Lee; W Yang; RG Paar, *Phys. Rev.*, **1988**, B37, 785.
- [19] RG Parr; W Wang, Density-Functional Theory of Atoms and Molecules; Oxford University Press: New York, **1994**.
- [20] R Neumann; RH Nobes; NC Handy, *Mol. Phys.*, **1996**, 87, 1.
- [21] T Koopmans. *Physica*; **1993**, 1, 104.
- [22] RG Pearson , *J.Am.Chem.Soc.*, **1963**, 85(22), 3533.
- [23] AD Becke., *J. Chem. Phys.*, **1993**, 98, 5648.
- [24] A Lesar; I Milosev, *Chem. Phys. Lett.*, **2009**, 483(4-6), 198.
- [25] RG Parr; L Szentpaly; S Liu, *J. Am. Chem. Soc.*, **1999**, 121, 1922.
- [26] PW Ayers; JSM Anderson; LJ Bartolotti, *Int. J. Quantum Chem.*, **2005**, 101, 520.
- [27] G Roos, S Loverix; E Brosens; K Van Belle; L Wyns; P Geerlings; *J Messens ChemBioChem.*, **2006**, 7, 981.
- [28] A.Smilde, R. Bro, R, P G: Multi-way analysis with applications in the chemical sciences. John Wiley & Sons Ltd, **2005**
- [29] R.G.Brereton, Chemometrics: Data analysis for the laboratory and chemical plant. John Wiley & Sons Ltd, **2003**
- [30] G Reich, *Adv Drug Deliver Rev.*, **2005**, 57, 1109.
- [31] S Garca-Mu noz ; T Kourti ; J MacGregor ; A Mateos ; G Murphy; *Ind Eng Chem Res.*, **2003**, 42, 3592.
- [32] LH Chiang ; LF Colegrove, *Chemometr Intell Lab.*, **2007**, 88, 143.
- [33] B Wise; N Gallagher, *J Process Contr.*, **1996**, 6, 329.