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Combined Computational and Chemometric study of Benzothiazole molecule by Semiempirical, Hartree – Fock (HF) and Density Functional Theory (DFT) at different levels of basis sets

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Abstract
Geometry of benzothiazole optimized at several computational levels: semiempirical methods (SEM), ab initio density functional theory (DFT) with Becke's three-parameter exchange functional and the gradient corrected functional of Lee, Yang, and Paar (B3LYP) functionals, and Hartree–Fock (HF) with different size of basis sets in gas phase. The bond lengths and mulliken charges were analyzed using principal component analysis (PCA) and hierarchical cluster analysis (HCA). The PCA and HCA results showed that the methods were divided into two groups: best and least methods, where PC1 > 0 for the best methods and PC1 < 0 for the least ones. i.e. semiempirical and DFT methods are best for the benzothiazole molecule for comparing the HF methods expect the HF/STO-3G in the case of bond lengths. From mulliken charges are divided by two groups according to basis sets one is with polarization and diffusion functions and other is no these functions. For the benzothiazole, the best methods are 7 to 10, 12 to 15, 18 to 21 and 23 to 26 from PCA and HCA results.

Keywords: benzothiazole, bond lengths, mulliken charges, principal component analysis (PCA) and hierarchical cluster analysis (HCA).

1. Introduction
Benzothiazoles are bicyclic ring system. A number of 2 aminobenzothiazole have been studied as central muscle relaxants and found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments [1]. Benzothiazole derivatives have been studied and found to have various chemical reactivity and biological activity. Benzothiazole ring made from thiazole ring fused with benzene ring. Thiazole ring is a five-member ring consists of one nitrogen and one sulfur atom in the ring.
Benzothiazole ring found to be possessing pharmacological activities such as anti- viral [2], anti- bacterial [3], anti- microbial [4] and fungicidal activities [5].They are also useful as anti-allergic [6], anti-diabetic [7], antitumor [8], anti- inflammatory [9], anthelmintic [10], and anti- HIV agents. Benzothiazoles show antitumor activity, the phenyl-substituted Benzothiazoles [11.13], while condensed pyrimido benzothiazoles and benzothiazole quinazolines show anti-viral activity. Substituted 6- nitro-and 6-aminobenzothiazoles show antimicrobial activity [14].
In addition, benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological properties. In last few years it was reported that benzothiazole, its bioisosteres and derivatives had antimicrobial activities against Gram-negative, Gram-positive bacterias (e.g., *Enterobacter*, *Pseudomonas aeruginosa*, *E. coli*, and *Staphylococcus epidermidis* etc.) andthe yeast (e.g., *Candida albicans*). Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. The basic structure (Fig.1) of benzothiazole consist of a benzene ring fused with 4, 5 position of thiazole. The two rings together constitute the basic nucleus 1, 3-benzothiazle.

2. Materials and methods

2.1 Computational Methods

The initial molecular geometry of the title compound were obtained by using the semiempirical AM1 [15], PM3 and PM6 [16], in gas phase. Afterwards, the HF with several basis sets was used optimization. Finally the structure was optimized by using DFT/6-311++G (d, p) method. The frequency analyses were carried out at the same level of theory. The absence of imaginary frequencies confirmed that the structures are true minima on the potential energy surface. The entire calculations conducted in the present work were performed in the Gaussian 09W package [17] program. By combining the results of the Gauss view program [18] with symmetry considerations, vibrational frequency assignments were made with a high degree of accuracy.

2.2 Chemometric Methods

Principal component analysis (PCA) and Hierarchical cluster analysis (HCA) are two important techniques in multivariate analysis to analyze data that corresponds to more than one variable. The main objective of PCA [19 – 21] and HCA are to study how the variables are related to one another, and how they work in combination to distinguish between multiple cases of observations. PC Auses an orthogonal transformation to convert a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables. The number of PCs is less than or equal to the number of original variables. This transformation is defined in such a way that the first principal component has the largest possible variance (that is, accounts for as much of the variability in the data as possible), and each succeeding component in turn has the highest variance possible under the constraint that it is orthogonal to (i.e., uncorrelated with) the preceding components. The principal components are orthogonal because they are the eigenvectors of the covariance matrix, which is symmetric. PCA is sensitive to the relative scaling of the original variables. Because of the lack of optimal data distribution (different units and variances), some preprocessing operation is required, as autoscaling (the scaled variables have zero mean and unity variance). Once the redundancy is removed, only the first few PCs are required to describe most of the information contained in the original data. HCA [20] is one of the most straightforward methods. It displays the data in 2D space, qualitatively, in a form of dendrograms with similarities among samples or variables. The distances between samples or variables are calculated, transformed into a similarity matrix ***S***, and compared. For any two samples *k* and *l*, the similarity index is

$$S_{kl} = 1.000 - \frac{d_{kl}}{d_{max}} \quad (1)$$

Where S_{kl} is an element of ***S***, d_{max} is the largest distance among each pair of samples in the data, and d_{kl} is the Euclidean distance among samples k and l. All chemometric methods were performed using software Ky-plot.

This article focuses on the use of Chemometric methods PCA (Principal Component Analysis) and HCA (Hierarchical Cluster Analysis) to determine: the best calculation methods for geometry of Benzothiazole and mulliken charges.

3. Results and Discussion

3.1 Molecular Geometry

The benzothiazole assumed as C1 point group of symmetry and the optimized geometrical parameters of the title compound is calculated according to the labeling of atoms as shown in the Figure 1. The most optimized bond lengths of this compound were calculated and shown in Table 1

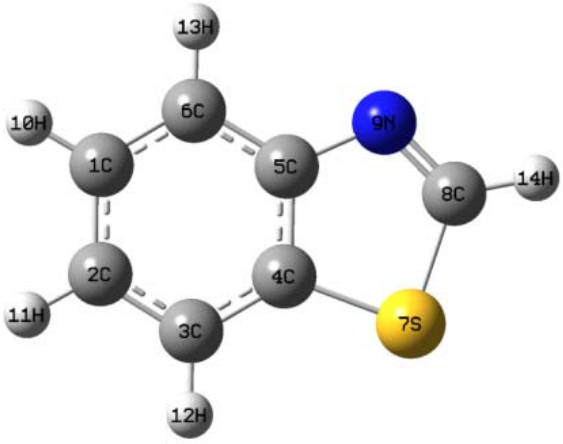

Fig 1: optimized geometrical structure of benzothiazole

Table 1: Bond length data (Å) for Benzothiazole

Method	C1-C2	C1-C6	C2-C3	C3-C4	C4-C5	C4-S7	C5-C6	C5-N9	S7-C8	C8-N9
1 .AM1	1.405	1.3853	1.3868	1.3957	1.4369	1.6942	1.4084	1.4071	1.7272	1.315
2 .PM3	1.400	1.387	1.387	1.394	1.417	1.750	1.397	1.426	1.768	1.312
3. PM6	1.409	1.393	1.396	1.392	1.422	1.745	1.404	1.424	1.800	1.299
4 .**HF/STO-3G**	1.402	1.376	1.377	1.396	1.395	1.744	1.4	1.443	1.749	1.293
5. **HF/3-2G**	1.393	1.377	1.381	1.379	1.388	1.805	1.384	1.409	1.836	1.263
6. **HF/6-31G**	1.3974	1.3811	1.3843	1.3849	1.3926	1.8096	1.3887	1.4031	1.8158	1.2688
7. **HF/6-31G+**	1.3991	1.3825	1.3857	1.3864	1.3929	1.8068	1.3894	1.4038	1.8148	1.2697
8. **HF/6-31G++**	1.3991	1.3825	1.3857	1.3864	1.3929	1.8068	1.3894	1.4038	1.8148	1.2697
9. **HF/6-31G+(d,p)**	1.4009	1.3777	1.3794	1.392	1.3935	1.7451	1.3946	1.389	1.7462	1.2669
10. **HF/6-31G++(d,p)**	1.4009	1.3777	1.3794	1.392	1.3935	1.7451	1.3946	1.389	1.7462	1.2669
11. **HF/6-311G**	1.3977	1.3801	1.3829	1.3844	1.3909	1.8044	1.3882	1.404	1.8146	1.2684
12. **HF/6-311G+**	1.3981	1.3809	1.3838	1.3852	1.3913	1.8056	1.3883	1.4041	1.8149	1.2683

13. **HF/6-311G++**	1.3981	1.3809	1.3838	1.3852	1.3913	1.8055	1.3883	1.4042	1.8148	1.2683
14. **HF/6-311G+(d,p)**	1.3995	1.376	1.3773	1.3907	1.3916	1.7442	1.3931	1.3886	1.7469	1.2641
15. **HF/6-311G++(d,p)**	1.3995	1.376	1.3773	1.3907	1.3916	1.7443	1.3932	1.3886	1.747	1.2641
16. **B3LYP/3-2G**	1.4049	1.3904	1.3949	1.3906	1.4131	1.8127	1.398	1.408	1.8644	1.2852
17. **B3LYP /6-31G**	1.4084	1.3937	1.3982	1.3956	1.4161	1.8187	1.4018	1.4062	1.845	1.2918
18. **B3LYP /6-31G+**	1.4102	1.3953	1.3997	1.3972	1.4164	1.8166	1.4023	1.4074	1.8403	1.2938
19. **B3LYP /6-31G++**	1.4102	1.3953	1.3997	1.3972	1.4164	1.8166	1.4023	1.4074	1.8403	1.2938
20. **B3LYP /6-31G+(d,p)**	1.4083	1.3903	1.3931	1.3994	1.4177	1.7528	1.4036	1.3899	1.766	1.2924
21. **B3LYP /6-31G++(d,p)**	1.4083	1.3903	1.3931	1.3994	1.4177	1.7529	1.4036	1.3899	1.7663	1.2923
22. **B3LYP /6-311G**	1.4066	1.3914	1.3956	1.3932	1.4132	1.8188	1.3994	1.407	1.8495	1.2893
23. **B3LYP /6-311G+**	1.4072	1.3921	1.3962	1.3942	1.4132	1.8189	1.3995	1.4076	1.8461	1.2896
24.**B3LYP /6-311G++**	1.4072	1.3921	1.3962	1.3942	1.4132	1.8188	1.3996	1.4077	1.8459	1.2897
25. **B3LYP /6-311G+(d,p)**	1.405	1.3865	1.3892	1.3962	1.414	1.7518	1.4008	1.3877	1.7652	1.2875
26. **B3LYP /6-311G++(d,p)**	1.405	1.3865	1.3892	1.3962	1.414	1.7519	1.4009	1.3877	1.7652	1.2876

3.2 PCA and HCA Results for Bond lengths

The main purpose of the Principal Component Analysis (PCA) is to determine a few linear combinations of the original variables which can be used to summarize the data set without losing information [22]. This is achieved by a linear transformation of the original data set of variables into a smaller number of uncorrelated principal components (PCs). Geometrically, this transformation represents the rotation of the original coordinate system and the direction of the maximum residual variance is given by the first principal component axis. The second principal component, orthogonal to the first one, has the second maximum variance and so on. In this way, projections conserving maximum amounts of statistical information can be plotted in order to show us a more detailed study of the data structure [23-25].

In the present research work, coupled HCA and PCA were employed for finding the best calculation methods for some property consists of simultaneous inspection of HCA dendrograms and 2D or 3D PCA plots and finding out what these plots have in common with respect to the closest neighborhood. These plots frequently exhibit clustering of methods or objects (molecules, bonds, etc.) according to some property.

Table 2: PCA Results for Bond Lengths

PCs	% Variance	% Cumulative variance
PC1	57.08	57.08
PC2	26.99	84.10
PC3	11.41	95.50
PC4	3.04	98.54
PC5	0.94	99.48

From table 2 (PCA results), the first three principal components describe 95.5% of the overall variance. Since almost all of the variance is explained by the first two PCs, their score plot is a reliable representation of the special distribution of the points for the data set studied Table 1. The most informative score plot and loading vectors for the first two principal components PC1 and PC2 are displayed in Fig.2 and 3. The PC1is alone responsible for the separation between the best and least methods. The methods were divided into two groups:one is best methods 1 to 4 and 16 to 26 in Figure 2 and another is least methods 5 to 15 in Figure 2, where PC1 > 0 for the best methods and PC1 < 0 for the least ones. i.e. semiempirical and DFT methods are best for the benzothiazole molecule for comparing the HF methods expect the HF/STO-3G.

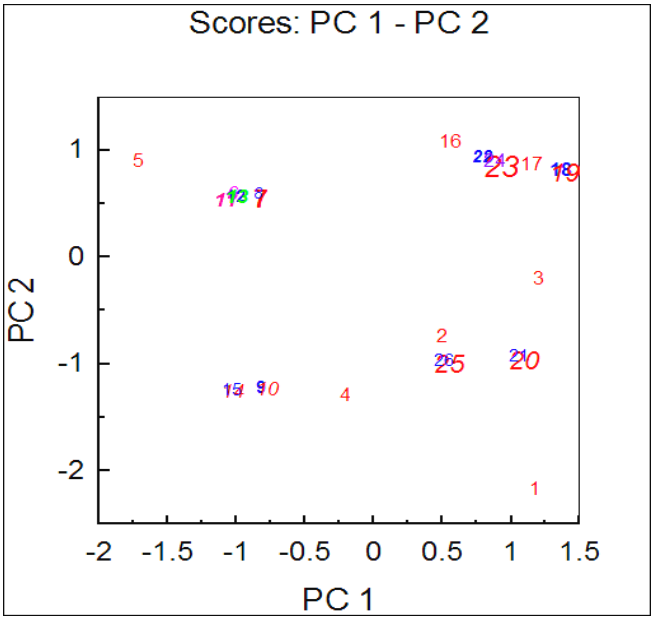

Fig 2: Score Plot for the twenty six methods.

According to Fig.3, PC1 can be expressed through the following equation:

$PC1 = 0.397[C_1\text{-}C_2] + 0.376[C_1\text{-}C_6] + 0.356[C_2\text{-}C_3] + 0.349[C_3\text{-}C_4] + 0.394[C_4\text{-}C_5] - 0.022[C_4\text{-}S_7] + 0.388[C_5\text{-}C_6] + 0.073[C_5\text{-}N_9] + 0.065[S_7\text{-}C_8] + 0.368[C_8\text{-}N_9]$ (2)

From Eq. (3) we can see that the best methods (PC1>0) can be obtained when we have higher values of all C-C bonds and C_8-N_9 bond, combined with negative C_4-S_7value and lower values of the C_5-N_9 and S_7-C_8. From this we conclude that all the C-C bonds in the benzene ring are differing from the thiazole ring bonds expect the C_8-N_9 bond.

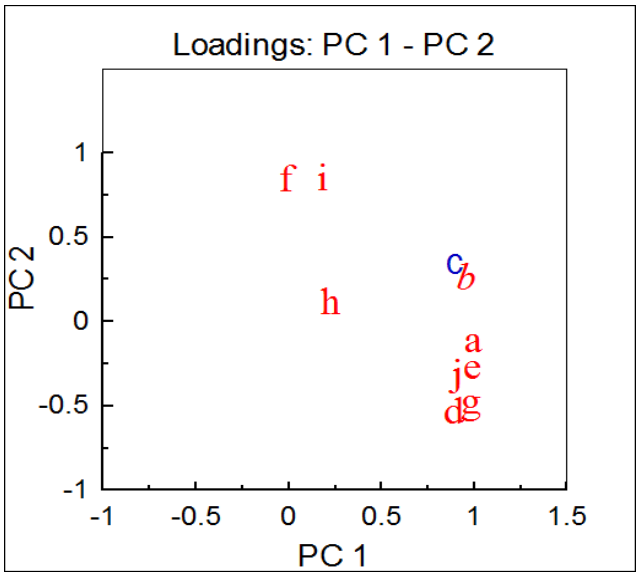

Fig 3: Loading Plot for the Ten variables responsible for the classification of twenty six methods studied: a = C1-C2, b = C1-C6, c = C2-C3, d = C3-C4, e = C4-C5, f = C4-S7, g = C5-C6, h = C4-N9, i = S7-C8, j = C8-N9

3.3 HCA Results for Bond Lengths

Hierarchical cluster analysis (HCA) was used in this work as it groups the compounds based on their similarity degree. In this technique, each compound is initially assumed to be a lone cluster and one similarity matrix is built, generally calculating the Euclidean distance among all of the objects. Then, the compounds are clustered together and treated as a single cluster and successive iterations lead to the total clustering of all compounds according to their similarity level generating a dendrogram [25].

Fig.4 shows our results obtained with HCA analysis. The horizontal lines represent the methods and vertical lines the similarity values between pairs of methods, a method and a group of methods and among groups of methods. The similarity value between the two classes of methods was 0.0 and this means these two classes are distinct. From Fig.4, we can see that the HCA results are very similar to those obtained with the PCA analysis. i.e, the methods studied was grouped into two categories: Group A is the best methods 1 to 4 and 16 to 26 in Table. 1 and Group B is the least methods 5 to 15 in Table. 1.

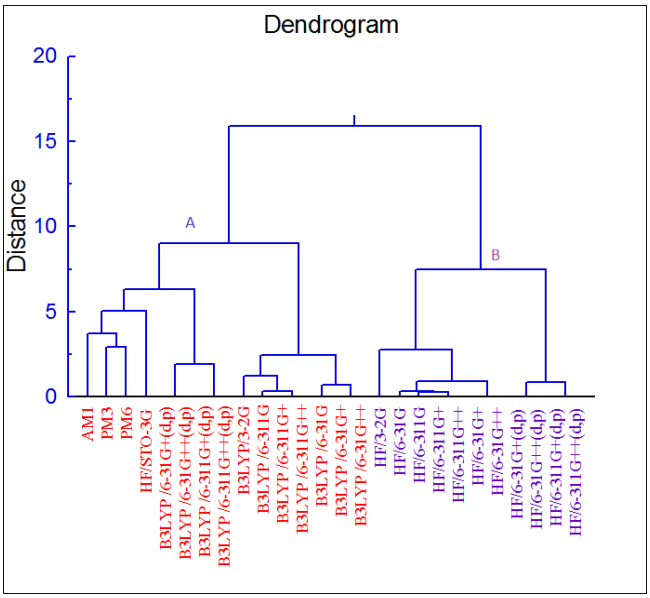

Fig 4: Dendrogram obtained for the twenty six methods studied in table I: Group A (Best) and Group B (Least)

3.4 The Mulliken Charges Calculation

The Mulliken procedure is the most common population analysis technique. In population analysis, the electrons in each molecular orbital are partitioned to each atom based on the probability that the electron is in an orbital on that atom at the end of the calculation the fractional occupation for each molecular orbital is summed to get a total atomic electron population for each atom [26]. Mulliken charges arising from the Mulliken population analysis provides a mean of estimating partial atomic charges from calculations carried out by the methods of computational chemistry, particularly those based on the linear combination of atomic orbitals molecular orbital method [27, 28]. The Mulliken charges of each carbon atoms for optimized Geometry of each molecule under investigation were calculated and gathered in Table 3.

Table.3 The mulliken charges at all carbon atoms for the Benzothiazole

Method	C1	C2	C3	C4	C5	C6	S7	C8	N9
1 .AM1	-0.0918	-0.1662	-0.0768	-0.3053	-0.0245	-0.1266	0.4348	-0.2625	-0.1614
2 .PM3	-0.0997	-0.0927	-0.0505	-0.2383	-0.0791	-0.0426	0.2303	-0.1999	-0.0310
3. PM6	-0.1391	-0.1391	-0.1186	-0.1243	0.0897	-0.1304	0.0025	-0.0091	-0.2617
4 .**HF/STO-3G**	-0.0672	-0.0563	-0.0694	-0.1106	0.0580	-0.0561	0.2420	-0.0567	-0.2472
5. **HF/3-2G**	-0.2447	-0.2267	-0.2304	-0.4805	0.3087	-0.2108	0.5619	-0.1981	-0.6020
6. **HF/6-31G**	-0.2216	-0.1849	-0.1969	-0.4033	0.1772	-0.1204	0.4943	-0.2237	-0.4393
7. **HF/6-31G+**	-0.3765	-0.0542	0.0845	1.4963	-1.7396	-0.8173	0.1268	0.1200	-0.0887
8. **HF/6-31G++**	-0.2906	-0.1125	0.08008	1.55218	-1.8384	-1.01159	0.13184	0.1864	-0.0606
9. **HF/6-31G+(d,p)**	-0.2638	-0.1183	0.0224	0.6398	-0.9529	-0.1621	-0.0826	0.1929	-0.1706
10. **HF/6-31G++(d,p)**	-0.1307	-0.0854	-0.1764	0.8373	-0.8233	-0.4588	-0.0485	0.2344	-0.1598
11. **HF/6-311G**	-0.1775	-0.1490	-0.1627	-0.3791	0.2246	-0.0418	0.3054	-0.1320	-0.4276
12. **HF/6-311G+**	-0.3462	0.0303	0.3599	3.0362	-2.2870	-1.7726	-0.4165	0.2541	-0.0577
13. **HF/6-311G++**	-0.5960	-0.2187	0.5295	2.6414	-2.7827	-1.2075	-0.6083	0.3623	-0.0404
14. **HF/6-311G+(d,p)**	-0.2026	-0.0140	0.0025	1.8414	-1.1442	-0.9716	-0.3813	0.2026	-0.0557
15. **HF/6-311G++(d,p)**	-0.3691	-0.1854	0.0697	1.5652	-1.3208	-0.6159	-0.5896	0.3325	-0.0451
16. **B3LYP/3-2G**	-0.1964	-0.1700	-0.2063	-0.3911	0.2825	-0.1667	0.5030	-0.2071	-0.5027

17. **B3LYP /6-31G**	-0.1530	-0.1042	-0.1622	-0.2851	0.15293	-0.0663	0.40220	-0.2077	-0.3286
18. **B3LYP /6-31G+**	-0.2786	0.0444	0.0386	1.2858	-1.3178	-1.0234	0.3909	-0.0392	-0.0714
19. **B3LYP /6-31G++**	-0.2373	-0.0710	0.2121	1.2586	-1.5502	-1.1234	0.4033	0.0327	-0.0413
20. **B3LYP /6-31G+(d,p)**	-0.1989	-0.0032	-0.0417	0.8502	-0.8453	-0.5348	0.1605	0.0288	-0.1138
21. **B3LYP /6-31G++(d,p)**	-0.1087	-0.0719	0.0049	0.9119	-0.8803	-0.7340	0.1611	0.1118	-0.0953
22. **B3LYP /6-311G**	-0.1631	-0.1396	-0.1424	-0.3575	0.1389	-0.0289	0.3148	-0.1807	-0.3103
23. **B3LYP /6-311G+**	-0.3255	0.0041	0.5962	2.8737	-2.5192	-1.5677	-0.3873	0.2234	0.0222
24.**B3LYP /6-311G++**	-0.4903	-0.0772	0.4685	2.7977	-2.9164	-1.2084	-0.4837	0.2953	0.0367
25. **B3LYP /6-311G+(d,p)**	-0.1883	-0.0619	0.2926	1.7185	-1.3888	-0.8837	-0.3716	0.1627	0.0277
26. **B3LYP /6-311G++(d,p)**	-0.3002	-0.0900	0.0854	1.7530	-1.5557	-0.6790	-0.4833	0.2607	0.0379

3.5 PCA and HCA for Mulliken Charges

From table 4, we can observe that almost all of the variance is explained by the first two PCs, their score plot is a reliable representation of the special distribution of the points for the data set studied Table 3. The score and Loading Plots are presented in Fig. 5 and 6 (PC1 vs PC2) and we can see that PC1 alone is responsible for the separation between the best and least methods. From Fig.5, we can see that the twenty six methods studied were separated into two groups: one is the best methods 7 to 10, 12 to 15, 18 to 21 and 23 to 26 in Table 3 and another is the least methods 1 to 6, 11, 16, 17 and 22 in Table 3, where PC1 > 0 for the best methods and PC1 < 0 for the least ones for benzothiazole.

Table 4: PCA Results for Mulliken Charges

PCs	% Variance	% Cumulative variance
PC1	73.10	73.10
PC2	13.37	86.47
PC3	6.64	92.98
PC4	3.07	96.05
PC5	1.81	97.87

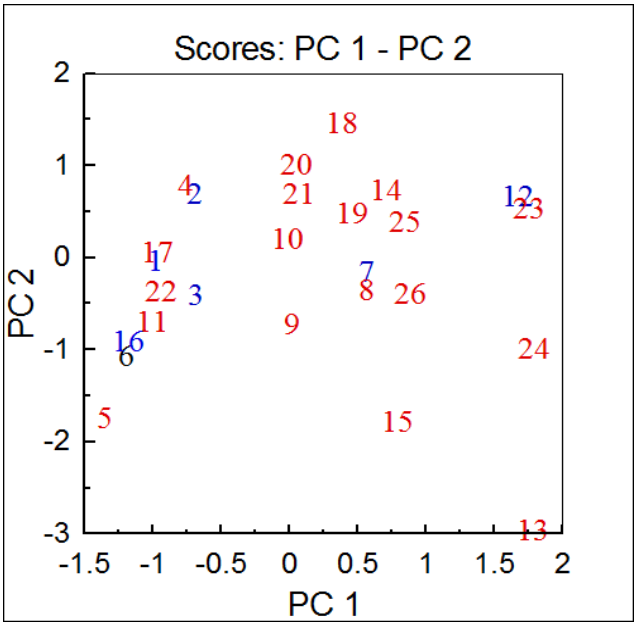

Fig 5: Score Plot for the twenty six methods studied in Table 3

The loading vectors for the first two principal components PC1 and PC2 are displayed in Fig. 6. According to Fig.6, PC1 can be expressed through the following equation: PC1 =– 0.289 [C1] + 0.178[C2] + 0.357[C3] + 0.387[C4] – 0.382[C5] – 0.355[C6] – 0.328[S7] + 0.349[C8] + 0.323[N9] (3)

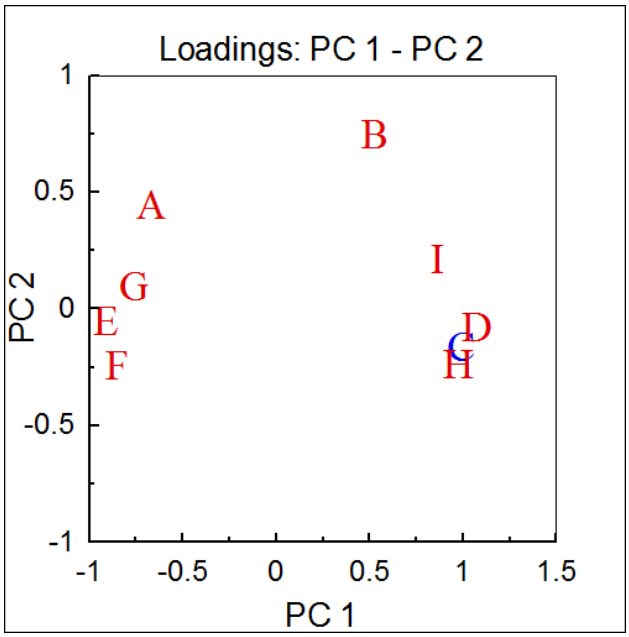

Fig 6: Loading Plot for the Nine variables responsible for the classification of twenty six methods studied: A = C1, B = C2, C = C3, D = C4, E = C5, F = C6, G = S7, H = C8, I = N9

From Fig.7, we can observe that the similarity value between the two classes of methods was 0.0 and this means that these two classes are distinct and also we found the HCA results are very similar to those obtained with the PCA analysis. i.e, the methods studied was grouped into two categories: Group A is the best methods 7 to 10, 12 to 15, 18 to 21 and 23 to 26 in Table 3 and Group B is the least methods 1 to 6, 11, 16, 17 and 22 in Table 3.

The methods 7 to 10, 12 to 15, 18 to 21 and 23 to 26 in Table 3 are including with diffusion and polarization function of basis sets. Diffusion functions are large size versions of s and p type functions and they allow orbital's to occupy a larger region of space. Basis sets with diffusion functions are important for system where electrons are relatively for from the nucleus and molecules with loan pair electron. The polarized functions basis sets allow orbital's to change size, but not change shape and with d functions added to heavy and atoms nitrogen and hydrogen can individually be reasonably well described entirely by s and p functions. So the above methods are best for benzothiazole. Because of have heavy atoms, nitrogen, sulfur and loan pair electrons present in the title compound.

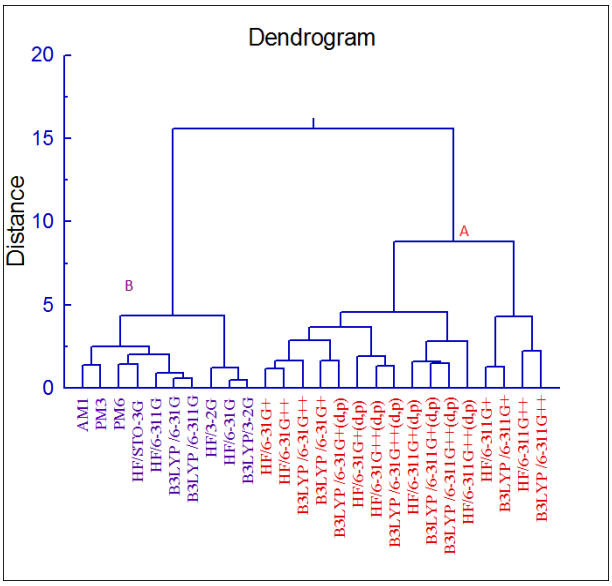

Fig 7: Dendrogram Obtained for the twenty six methods studied in table 3 Group A (Best) and Group B (Least)

4. Conclusions

Chemometric analysis of the computational results of bond lengths for benzothiazole clearly shows that DFT and SEM best methods with different basis sets comparing to HF method with different basis sets from PCA results. Besides, grouping of bonds into clusters is in accordance with structural properties. The methods studied were grouped into two categories from HCA results: Best methods (1 to 4 and 16 to 26) and least methods (5 to 15). From mulliken charges are divided by two groups according to basis sets one is with polarization {6-311G (d, p) and diffusion functions {6-311++} and other is no these functions. For the benzothiazole, the best methods are 7 to 10, 12 to 15, 18 to 21 and 23 to 26 from PCA and HCA results.

5. References

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