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Computational Design of Anticancer Drugs Bicyclic, Tricyclic and Heterocyclic Alkanes in Proton Affinity Reaction

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ABSTRACT

The atomistic details of the interaction between polycyclic and heterocyclic anticancer drug, realistic model for drug delivery by quantum mechanical modeling Criteria are developed and discussed that lead to the design of a new polycyclic and heterocyclic anticancer drug, which should have low toxicity but high biological selectivity and activity when attacking the DNA of tumor cells. Study of structural and thermodynamic properties of some polycyclic and heterocyclic Alkanes in proton affinity reaction using quantum mechanic methods are the main purposes of this thesis. Some structural parameters such as bond length, bond Angle and torsion Angle and some thermodynamic parameters such as enthalpy, Gibbs free energy, thermal energy was calculated using primary calculations of (HF) and density functional theory (DFT) with basis sets of 6-311^{++}G** and 6-31G**and comparison between stability of reactants and products was carried out using applied thermodynamic parameters and principles of quantum mechanic such as maximum hardness principle (M.H.P) and minimum electrophilicity principle (M.E.P). Obtained results show that calculation of thermal energy is more appropriate than other thermodynamic parameters since in calculation of enthalpy and Gibbs free energy with two methods of HF and B3LYP and two applied basis sets, none of products were more stable than reactants but in calculation of thermal energy all products were more stable with all methods and basis sets. In using of maximum hardness principle, B3LYP method is more appropriate than HF Method since its influence from base set is less and shows more stable products. For minimum electrophilicity principle, choosing the HF method is better than B3LYP method with 6-311++G** base set since more molecule would be stable.

Keywords: Polycyclic, Heterocyclic, Enthalpy,; Thermal energy

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INTRODUCTIONS

The proton conveyer reactions are very important in chemical processes and bio molecular organisms and containing the most reactions which have been catalyzed with enzyme. Also protonation of chemical groups is related to their bio molecular operation like side chain of amino acids. Investigations about molecular protonation of poly pyridine are very interesting in biological and pharmacological studies because protonation is much related to biological activity [1]. Protonation and de protonation in a chemical group are specified by pK_a, pK_a of a molecule depends on surrounding molecular environment and its determination is possible empirical but is not a simple work.

In this project the structural and thermodynamic properties of 12 molecules have been investigated in proton affinity reaction[2]. These investigations have been done using the parameters of bond length, bond angle and torsion angle for structural properties and parameters of enthalpy, thermal energy, Gibbs free energy, hardness and electrophilicity for thermodynamic properties by HF and B_3LyP methods and two basis sets of 6-31G** and 6-311^{++}G**[3].

MATERIALS AND METHODS

COMPUTATIONAL METHOD

Calculations are based on periodic density functional theory adopting all-electron Gaussian-type basis functions of polarized double-ζ quality and the B3LYP hybrid functional. The proton affinity reactions of polycyclic and heterocyclic alkans were carried out for investigating the electrophilicity and thermodynamic structural properties using density functional hybrid method and ab initio method of HF by Hyper Chem, Chem Draw, Gauss view and Gaussian 03 software. Studied molecules are 6 bicyclic, 3 tricyclic and 3 heterocyclic alkanes[4].

Since in an exothermic reaction, products are more stable than reactants so the stability of products (A_2) in proportion to reactants (A_1) has been investigated based on common principles in quantum mechanics. These principles contain maximum hardness principle and minimum electrophilicity principle. Also the thermal energy, Gibbs free energy and enthalpy of reactions were investigated. The molecules structures were optimized using DFT methods and basis sets of 6-31G** and 6-311^{++}G**. Structural properties such as bond length, bond angle and torsion angle of molecules also thermodynamic properties such as enthalpy, thermal energy, Gibbs free energy and energy of HOMO and LUMO orbitals then electrophilicity and hardness of molecules were calculated. Calculated amounts of reactants and products were compared and were used for determining the hardness changes $(\Delta\eta)$, enthalpy ΔH , Gibbs free energy (ΔG) and thermal energy (ΔQ). Products and reactants have been shown with A_2 and A_1 respectively[5].

Optimization of molecules by software

Some reactants such as tricyclic and heterocyclic alkanes and their products were drew in hyper chem. and optimized by semi empirical method of *PM_3*. The vibrational frequency of bicyclic alkanes was studied in hyper chem. Also these molecules were deprotonated in hyper chem. and their frequency was studied as a reactant. An acceptable structure is a structure that its all vibrational frequencies are positive because the negative frequency is a sign of unstable structure[6]. After optimization, the calculations were carried out on molecule by Gauss view and Gaussian software and using the ab initio methods of HF or density functional theory (DFT) and proper basis sets and then structural and thermodynamic properties of them were obtained[7].

RESULTS AND DISCUSSION

Investigation results of thermodynamic properties containing enthalpy, Gibbs free energy, thermal energy and calculation results of hardness and electrophilicity by different methods and basis sets are shown in tables 1-3.

A is bicycle (1, 1, 1) pentane, B is bicycle (2, 1, 1) hexane, C is bicycle (2, 2, 1) heptane, D is bicycle (2, 2, 2) octane, E is bicycle (3, 1, 1) heptane, F is bicycle (3, 2, 1) octane, G is tricycle (1, 1, 1, 1) hexane, H is tricycle (1, 1, 1, 0) pentane, I is tricycle (2, 2, 1, $0^{2,6}$) heptane, J is 1, 3 di azo bicycle pentane, K is 1, 4 thia bicycle heptane and L is 1, 3 di oxa bicycle pentane.

Table.1 The enthalpy, Gibbs free energy, thermal energy, hardness and electrophilicity changes of all molecules in proton affinity reaction by HF/6-31G method (based on Hartree unit)**

Molecule	ΔH	ΔG	ΔQ	Δη	$\Delta\omega$
A	-193.89	-193.89	-0.6273	-0.0050	-0.0031
B	-0.3094	-0.2430	-0.6285	-0.0134	0.0012
C	-0.3732	-0.0059	-0.6256	0.0105	0.0037
D	0.0129	0.0149	-0.6187	0.0310	0.0003
E	0.0137	0.0143	-0.6209	0.2407	-0.6092
F	-0.0895	0.0152	-0.6267	0.0245	0.0061
G	0.0175	0.0217	-0.5165	0.0891	0.0009
H	-0.2234	0.0462	-39.6495	0.0728	-0.0051
I	0.0133	-0.0050	-0.6751	0.0126	0.0028
J	0.0170	0.0170	-0.5802	-0.0463	0.0112
K	0.0146	0.0146	-0.6195	-0.0094	-0.0067
L	0.0143	0.0143	-0.6118	-0.0719	0.0679

Table2. The enthalpy, Gibbs free energy, thermal energy, hardness and electrophilicity changes of all molecules in proton affinity reaction by HF/6-311^{++}G method (based on Hartree unit)**

Molecule	ΔH	ΔG	ΔQ	Δη	$\Delta\omega$
A	-2449.0	-193.92	-0.0627	0.0190	-0.0110
B	-0.3098	-0.0060	-0.6278	0.0107	0.0042
C	0.0143	-0.0050	-0.5958	0.0137	-0.0056
D	0.0129	0.0152	-0.6187	0.0320	-0.0603
E	0.0137	0.0144	-0.6209	0.0257	0.0129
F	0.0138	0.0152	-0.6268	0.0249	0.2727
G	0.0173	0.0214	-0.5111	0.0515	0.0263
H	0.0462	0.0454	-39.654	0.0184	0.0093
I	-0.3238	-0.0051	-0.6355	0.0142	0.0065
J	0.0169	0.0195	-0.5776	-0.0113	-0.0078
K	-0.0053	0.0155	-0.6192	-0.0184	-0.0069
L	0.0143	0.0145	-0.6120	-0.0450	-0.1559

Table3. The enthalpy, Gibbs free energy, thermal energy, hardness and electrophilicity changes of all molecules in proton affinity reaction by B_3L_yP/6-31G method (based on Hartree unit)**

Molecule	ΔH	ΔG	ΔQ	Δη	$\Delta\omega$
A	-0.2298	-195.24	-0.6626	-0.0011	-0.0041
B	-0.0268	-0.2243	-0.6652	0.0242	0.0085
C	0.0128	-0.0056	-0.6480	0.0271	-0.0422
D	0.0173	0.0211	-0.6656	0.0685	0.0412
E	0.0133	-0.0061	-0.6581	0.0362	0.0136
F	0.0132	-0.0055	-0.6637	0.0363	0.0150
G	0.0140	-0.0121	-0.4332	0.1049	-0.0198
H	0.0439	0.0431	-39.965	0.0085	0.0006
I	-0.3046	-0.0058	-0.6710	0.0156	0.0054
J	0.0135	-0.0102	-0.6601	-0.0778	0.0860
K	-0.0124	0.0152	-0.6563	0.0052	-0.0206
L	0.0132	0.0133	-0.6440	0.3810	-0.0033

Table4. The enthalpy, Gibbs free energy, thermal energy, hardness and electrophilicity changes of all molecules in proton affinity reaction by B_3L_yP /6-311^{++}G method (based on Hartree unit)**

Molecule	ΔH	ΔG	ΔQ	Δη	$\Delta\omega$
A	-0.2294	-195.29	-0.6585	0.0311	0.0191
B	0.0129	-0.2240	-0.6665	0.0248	0.0118
C	-0.0169	-0.0064	-0.6664	0.0262	0.0133
D	0.0135	0.0133	-0.6549	0.0398	-0.0409
E	0.0132	-0.0072	-0.6577	0.0353	0.0175
F	-0.0068	-0.0047	-0.4912	0.0199	0.0233
G	0.0139	-0.0110	-0.5604	0.0575	0.0121
H	0.0438	0.0441	-39.972	0.0095	0.0013
I	0.4384	-0.0055	-0.6733	0.0243	0.0121
J	0.0134	-0.0059	-0.6611	-0.0349	0.0696
K	0.0140	0.0153	-0.6554	-0.8849	0.0054
L	0.0133	0.0140	-0.6449	0.0431	0.0110

The effect of methods and basis sets on bond length

The bond length of all studied molecules in proton affinity reaction are changed except 4 bicyclic molecules of (A, B, C, D) which have constant bond length. Bicycles of E and F, tricycles and heterocyclic have changeable amounts and the bond length is affected by kind of method or basis set and changes. For seven initial molecules the bond length is decreased and for other molecules it increased. In this case the bond lengths are constant and are not affected by kind of method or basis set. HF method with basis set of 6-311$_{++}$G** is more proper because the bond length of molecules in case is constant and is not affected by kind of methods or basis sets.

For bicycle molecules of (A, B, C, D, F) and tricycle of G the bond angles are constant and do not depend on method and basis sets. Amounts of bond angles for bicycle of E are different in HF method with 6-311^{++}G** basis set in proportion to other methods and basis sets. The bond angles of H and L Tricycles also J, K and L heterocyclic are affected by methods or basis sets and is different.

All molecules have constant bond angles and are not affected by method or basis set.

The proton affinity reaction affects on molecules stability and changes the bond angles. The bond angles of bicycles in state become larger by different methods and basis sets and intra molecular repulsion is reduced and molecule become more stable and kind of method or basis set does not affect on it. In tricycles and heterocyclic, the kind of

method or basis set affects on bond angles and in state, the angles become larger in different methods and basis sets but we can not say which method or basis set is better because the angles changes in different methods and basis sets are changeable.

The effect of methods and basis sets on torsion angle

Except bicycles of A, B and C, the angles of other bicycles in one of methods are different with other methods and basis sets. Tricycle alkanes have approximately constant angles but have larger amounts in B_3LyP method with basis set of 6-311^{++} G**. Heterocyclic alkanes have changeable angles and kind of method and basis set affect on it.

All molecules in this state have constant angles in different methods and basis sets and angle is not affected by method or basis set.

The torsion angles of all molecules were changed in proton affinity reaction.

CONCLUSION

In this project the proton affinity of some poly cyclic and heterocyclic alkanes was investigated using the ab initio (HF) and density functional theory (DFT) methods. Also the proper method and basis set was studied for each concepts of enthalpy, Gibbs free energy, thermal energy, hardness and electrophilicity. Using of enthalpy and Gibbs free energy are not recommended for investigation of products stability because the enthalpy and Gibbs free energy changes of products are positive in proportion to reactants. Using the thermal energy in stability calculation of products in proportion to reactants is a proper way and difference in method and basis set dose not effect on results. In B3LYP method for investigating the product stability (hardness), more molecules became more stable and the kind of basis set has no effect on molecules numbers and B3LYP method is recommended. For investigating the electrophilicity, the method of HF with basis set of 6-311^{++}G** is proper.

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