JTE
HCMUTE
ISSN: 2615-9740

JOURNAL OF TECHNICAL EDUCATION SCIENCE
Ho Chi Minh City University of Technology and Education
Website: https://jte.edu.vn
Email: jte@hcmute.edu.vn

Computational dertermination of protonation for aromatic derivatives

Tam Minh Le[*1], **Hung Thanh Le**[2], **Giang Tien Nguyen**[1]
[1]*Department of Chemical Engineering, University of Technology and Education, HCMC, Vietnam*
[2]*Department of Chemical Engineering, University of Technology, HCMC, Vietnam*

[*]Corresponding author. *Email: tamlm@hcmute.edu.vn*

ARTICLE INFO

Received:	08/05/2023
Revised:	31/05/2023
Accepted:	01/06/2023
Published:	28/06/2023

KEYWORDS

Protonation;
Aromatic derivatives;
Computational chemistry;
Geometry optimization;
Transition state.

ABSTRACT

Protonation is an important process relating to various fields, such as biological reactions, and organic chemical synthesis. The determining position of protonation has been involved many challenging issues which are usually impossible to directly predict the positions of attaching protons from structures of molecules. However, predicting positions of protonation for aromatic rings is particularly important since it decides which form is preferred in the main products. For this reason, solving this task has been interesting for chemists since last decades with various studies carried out. Many results have been achieved in this field from both experimental and computational efforts. In the present work, protonation of three aromatic derivatives were investigated via the computational approach in which geometry configuration of relevant protonated molecules were optimized using the molecular modeling method. The results showed that protonation was strongly influenced when groups OH-, CH_3-, and NH_2- appear in aromatic derivatives with three cases studied including phenol, aniline and toluene.

Doi: https://doi.org/10.54644/jte.77.2023.1401

1. Introduction

Due to the rapid development of computer technology [1], since the end of 20th century large quantum chemistry problems have been solved with the assistance of different computing methods [2]. Recently, similar task have been also effectively investigated based on high-speed personal computers or workstations [3]. Therefore, developing software applications of quantum chemistry and theoretical chemistry (computational chemistry) implemented on PC has been quickly developed worldwide. Some well-known commercial software have been used in the field of applied informatics in chemistry, for instance Q Chem [4], QMCPACK (Monte Carlo based) [5], Hyperchem [6], Gaussian [7], etc.

Professional software Gaussian is considered as an important tool for molecular modeling which can be used to study many physical and chemical properties of molecules. In addition, Gaussian has the advantage of being easy to use and creating an INPUT system for many different calculation options. In general, it could be difficult for researchers who are just starting to approach the calculations of quantum chemistry. Several typical calculation methods are implemented in Gaussian, including semi-empirical, *ab*-initio method, DFT (Density Functional Theory), and Molecular Mechanics, etc.

The Molecular Mechanics (MM+) method is a semi-classical or empirical method, based on a parameterized force field rather than a wave function and molecular orbitals. The equations of the MM+ method are classical in nature and the force fields are generally determined from spectral data. However, the data obtained from ab initio calculations can also be further used for this method. The MM+ method is a fairly fast calculation method and is good for optimizing geometry, especially large molecules such as nucleotides, proteins which *ab*-initio methods or other semi-empirical methods are not applicable.

In this work, Gaussian was utilized to study protonation of different organic compounds. The benzene-type aromatic ring is a very stable closed conjugate ring and has relatively high aromatization energy, for instance carbo-benzene [8]. For an aromatic compound like benzene, for example, the substitution reaction is more likely than the addition reaction. The substitution reaction at the aromatic ring can be electrophilic S_EAr, nucleophilic substitution S_NAr or radical substitution S_RAr. However, because the aromatic ring has a high electron density and easily interacts with electrophilic particles, the most characteristic and common substitution reaction in aromatic compounds is the electrophilic substitution. Theoretically, the reaction between aromatic compounds and H^+ can occur by three different mechanisms including single-stage mechanism, single-molecule two-stage mechanism, and bimolecular two-stage mechanism. Experimental results show that most of the electrophilic substitution reactions in aromatic nuclei occur according to the σ complex formation mechanism as described in Fig. 1. [9].

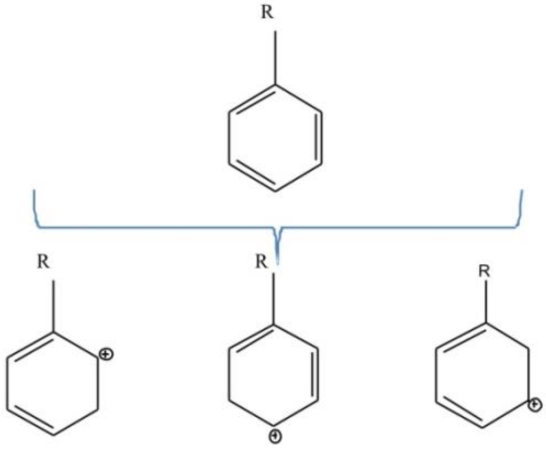


Figure 1. *Protonation of aromatic rings - possible attacked positions*

Effects of substituent in aromatic rings on electrophilic substitution reactivity

The kinetic and position of the electrophilic substitution reaction in the aromatic nucleus depends on many factors: The structure of the aromatic compound, the structure of the electrophilic agent, the reaction conditions, etc. Herein, we focused on the influence of the substituent to the attack position of the electrophilic agent. In general, an existing substituent in the aromatic nucleus can activate or deactivate the aromatic nucleus, i.e. it can increase or decrease the electrophilic substitution rate compared with the case of benzene. On the other hand, that substituent can cause preferability for other substituents to enter the ortho-, para- or meta-positions. That is mainly decided by the natural properties of that substituent. In fact, substituents with positive conjugation effect and positive inductive effects orient the new substituent to preferentially enter the ortho- and para-positions. Otherwise, substituents that have a negative conjugation effect along with a negative inductive effect or only with a directional negative effect on the substituent give preference to the meta- position. Between the two types of orientation groups mentioned above, there are also intermediate groups. Therefore, preferred positions for three derivatives can be expected as mentioned in Table 1.

Table 1. *Possible protonation for different aromatic derivatives*

compounds	R- group	Effects	Preferred positions
Phenol	OH-	+C, +I	ortho- , para-
Toluene	CH_3-	+C, +I	ortho- , para-
Aniline	NH_2-	+C, +I	ortho- , para-

In this work, we conduct optimization for geometry configuration to find out the energy of transition state (abbreviated as TS) where the three substances above react with H+ to form σ complexes. If TS has the lowest energy, then the related reaction mechanism will be favored for the formation of that species. As a consequence, the formed TS would determine the predominating product.

2. Calculation method

The calculation were carried out using Gaussian program, in which the method *hf/3-21g*** was used for configuration optimization. The result contains information about energy, bond angle, bond length, and charge distribution. For instance, a case study of toluene was simulated and the results were described as follows.

In the **Results and discussion** section, all calculated steps will be not shown (due to limited space reason). Appendix will be provided upon request.

- Bond length and bond angle

B1=1.38775029
B2=1.38707268
B3=1.37037709
B4=1.37037342
B5=1.38774497
B6=1.06879442
B7=1.06818466
B8=1.06849504
B9=1.0684949
B10=1.06818485
B11=1.49878009
B12=0.95076565
B13=0.95076578

A1=120.11290796
A2=116.48456113
A3=125.92071183
A4=120.88438979
A5=119.55797633
A6=120.40218953
A7=121.76746782
A8=121.74834188
A9=120.40248498
A10=117.03942098
A11=121.34023782
A12=121.34058472

D1=0.00026182
D2=0.00024723
D3=-0.00041328
D4=179.99987991
D5=179.99958394
D6=-179.99864962
D7=179.99893807
D8=179.99966656
D9=179.99957234
D10=90.02762334
D11=-89.97584036

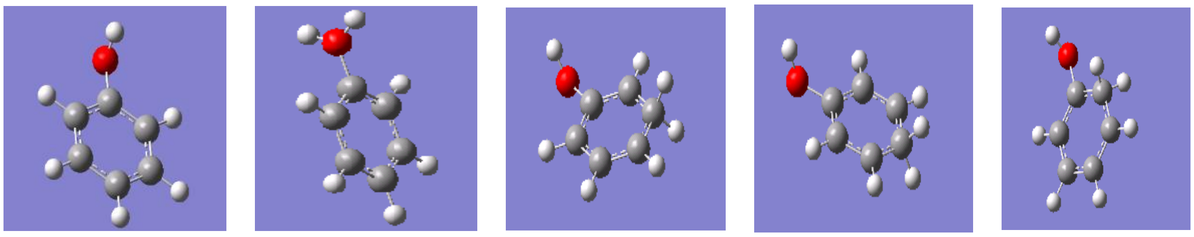
- Mulliken atomic charges:

1	C	-0.121115
2	C	-0.129613
3	C	-0.128200
4	C	0.215788
5	C	-0.128201
6	C	-0.129613
7	H	0.218795
8	H	0.220001
9	H	0.219050
10	H	0.219050
11	H	0.220001
12	O	-0.494056
13	H	0.409056
14	H	0.409056

3. Results and Discussion

3.1. Study on protonation of Phenol

The formation of intermediate complexes can occur according to three directions in aromatic ring and oxygen in OH^- group as seen in Fig. 2.



phenol	*O in OH group*	*meta-*	*para-*	*ortho-*
E(RHF)=-303.89	E(RHF)=-304.23	E(RHF)=-304.20	E(RHF)=-304.23	E(RHF)=-304.22

Figure 2. *TS complexes forming from reaction between* H^+ *and phenol (E(RHF) in [kcal/mol])*

From the results in Fig. 2, it can be seen that the energy of the intermediate complex corresponding to the para-position is the most stable because it has the smallest RHF energy, followed by the ortho- and then meta- positioned-products. This can be explained due to the fact that the OH^- group has a positive conjugation effect (+C), it repels electrons, making the negative charge density at ortho- and para- richer than that of meta-position. Therefore, the corresponding carbocation of the ortho- and para- forms are more stable than the meta-form. Particularly comparing the formation of two forms ortho- and para-, para- is more stable because the OH group has steric effects, the carbocation in the ortho-form is less stable than that of para-. In addition, $R\text{-}OH_2^+$ is also formed in large quantities because oxygen is electron-rich agent, it is also a negatively charged center. In summary, the priority of the reaction when adding H^+ to the aromatic ring follows the order para-, then ortho-, and finally meta-form. The calculated results are in good agreement with the theory of organic chemistry on the basis of effect groups. In particular, this conclusion shares similarity to a report of Hartmann *et al*. who found that the para-position could be dominated up to 80 percentage while ortho- and meta- derivatives could be formed about 67 and 8% [10].

3.2. Protonation of toluene

From the results of Fig. 3, we see that the energy of the intermediate complex corresponding to the para- form is the most stable, followed by the ortho- and finally the meta- form. In fact, group CH_3- has a positive inductive effect (+I), this effect makes the density of positive charge concentrated at the two positions (ortho- and para-) larger than the meta- position. Since H^+ prefers to attack sites with high charge density, the carbocation is in the most stable as para- form. In addition, CH_3- causes a steric effect that prevents H^+ from attacking the ortho- position, so the ortho- carbocation is less stable than that of para-. Meta-position has the lowest charge density so that it is the hardest to form. This conclusion gained a good agreement with the report of Esteves-López *et al.* who experimentally proved protonated priority of toluene and benzene [11].

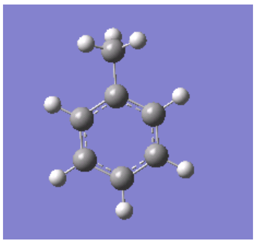
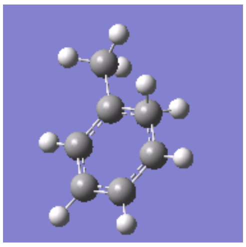
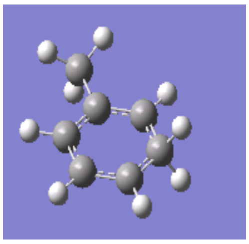
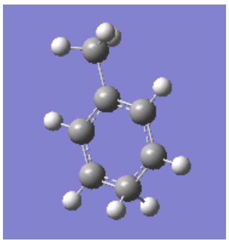
toluene	*ortho-*	*meta-*	*para-*
			
E(RHF)= -268.28	E(RHF)=-268.60	E(RHF)=-268.59	E(RHF)=-68.60

Figure 3. *TS complexes forming from reaction between H+ and toluene (E(RHF) in [kcal/mol])*

3.3. Protonation of aniline

Similar to the previous cases, carbocation σ can be formed corresponding to three positions in the benzene ring. Results of calculation were summarized in Fig. 4.

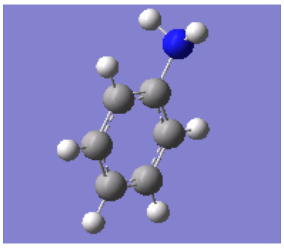
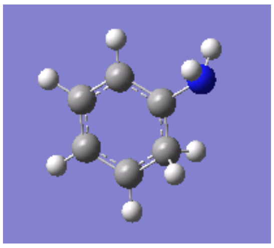
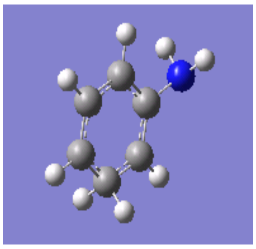
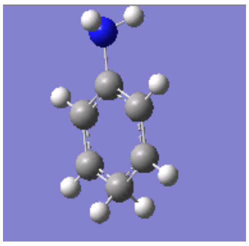
aniline	*ortho-*	*meta-*	*para-*
			
E(RHF) = -284.18	E(RHF) = -284.54	E(RHF) = -284.49	E(RHF) = -284.55

Figure 4. *TS complexes forming from reaction between H+ and toluene (E(RHF) in [kcal/mol])*

Several conclusions can be derived when comparing RHF values of the formed carbocation σ. At first, H^+ is most susceptible to nitrogen in the NH_2- group because N has the greatest density of negative charge. As reported by Smith *et al.*, almost 90% of aniline molecules were found to be protonated on the nitrogen atom [12]. However, Fig. 4 just presents results relating to protonation of aromatic ring. Herein, the intermediate complex corresponding to the para- form is the most stable, followed by the ortho- and lastly the meta- from. This conclusion can be explained base on the fact that in the case of aniline, the -I effect causes the charge density to concentrate mainly at the meta- site, however, since the system is in the conjugated state, +C is also dominates. For that reason, it is preferred for H^+ positions to the ortho- and para- than the meta- positions. The para-form is more stable than the ortho-form because the carbocation in the ortho-form can create steric effects by the NH_2- group.

4. Conclusions

In summary, the obtained results were completely consistent with general theory of protonation for aromatic compounds. For further utilization, however, it is necessary to conduct this research along with experiments to get more accurate conclusions. Above all, the rapid development trend of computational chemistry has been proved as a powerful tool which helps to save time and investment cost in discovery synthesis methods for novel compounds, in particular for pharmaceuticals, proteins, amino acids. Using the computational approach, many physical properties can be predicted such as geometry, energy of formation, transition state, and therefore it can be considered as a powerful tool for mechanism studies.

Acknowledgments

The authors would like to thank supports from HCMUTE and HCMUT.

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Tam Minh Le
Dr. -Eng. Tam Minh Le. PhD at Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany. Postdoctoral research at Vietnam Academy of Science and Technology. Editorial Board Member of JCERU journal. Expertise in the fields of advanced materials, enantiomer separation, crystallization, chromatography, process analytical technology (PAT), chemical and bio-process engineering. Email: tamlm@hcmute.edu.vn

Hung Thanh Le.
Dr. Hung Thanh Le is a lecturer in Ho Chi Minh City University of Technology with more than 20 year experiences in the field of chemical engineering. He got his Dr Degree in Belgium. His expertise includes organic chemical engineering, computational chemistry. Recently, he has many interesting researches relating to organic chemistry, computational chemistry, chemical engineering, computer utilization in chemical engineering. Email: lthung@hcmut.edu.vn

Giang Tien Nguyen.
Dr. Nguyen Tien Giang got his bachelor (2012) and master degree (2015) at the department of analytical chemistry from Ho Chi Minh City University of Science. After achieving his Ph.D degree from Korea University of Science and Technology (2021), he returned to Vietnam and working as a lecturer at Faculty of Chemical and Food Technology, HCMC University of Technology and Education. His research is concentrating on the synthesis of porous materials, surface modification, and thermal energy storage. Email: ntgiang@hcmute.edu.vn