Computational modeling of inclusion complex between aromatic amine and calixarene analogs using Semiempiric Quantum Method (SQM)

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Abstract. PM3 Semiempiric Quantum calculation has been done in this research by using Gaussian 2009 Rev. D 01 software package to explore the capability of Calixarene and its analogs for aromatic amine extraction. The Calixarene analogs used in this research are Calixpyrrole, Calixpyridine, Thiacalixarene, Heterocalixaromatic, Calixcarbazole and Calixnaphthalene; and the aromatic amine used in this research are Aniline, 4-Chloroaniline, Toluene-2,4-diamine, 2-Naphtylamine, 4,4'-Metylenbis(2-chloroaniline), 4,4'-Metylenedianiline, N-Nitrosodiphenylamine, Benzidine, 2-Aminobiphenyl, 2-Amino-1-methyl-6-phenylimidazo[4,5-b] Pyridine, 3-Trifluoromethylaniline, p-Phenyldiamine, o-Toluidin, 4-Chloro-o-toluidin. The most suitable host molecule of calixarene analogs for extraction of aromatic amine compounds are Calixnaphthalene and Calixpyridine because all of aromatic amine compounds form inclusion complex with them spontaneously shown by negative value of binding energy.

1. Introduction
Aromatic amines and N-nitroso derivatives are carcinogenic compounds [1-4]. Aromatic amines are widely used as raw materials or as intermediates in the manufacture of chemicals such as pesticides, drugs, dyes, polymers, surfactants, cosmetics, and corrosion inhibitors [5,6]. Because these chemical wastes are discharged into the atmosphere and aquatic environment, these wastes have the potential to be accumulated and form dangerous environmental pollutants [7]. Thus, it is necessary to develop a material that can extract this waste very well. One type of material that can be used is organic supramolecular material, i.e. Calixarene. Over the past two decades, calixarene has attracted the attention of many researchers as receptor in the field of supramolecular chemistry [8-13]. This is because calixarene is easy to be synthesized and it also has good selectivity to the guest molecules [14-16]. Calixarene has several analogues that also act as host materials with specific chemical properties, such as Calixpyrrole [17], Calixpyridine [18], Thiacalixarene [19], heterocalixaromatic [20], Calixcarbazole [21], and Calixnaphthalene [22]. Erdemir et al. have reported the use of calixarene as a carrier material for the extraction of carcinogenic compounds of aromatic amines, i.e. benzidine, p-chloroaniline, and α-naphthlamine from aqueous solutions [7]. However, to the best of our knowledge, until now there are...
no researchers that have reported and studied the ability of calixarene and its analogs to extract the other carcinogenic compounds of aromatic amines beside those three compounds. In this research, computational investigation has been carried out by using PM3 semiempiric quantum method to explore the properties of Calixarene and its analogs as potential material for extracting of aromatic amine compounds.

2. Methods
In this research, we applied a computational method which is divided by three sections. First, construct the host and guest molecule, Second, molecular docking simulation, and Third, PM3 Semiempiric Quantum calculation.

2.1. Construct the host and guest molecule
Guest molecules used in this research are aromatic amine compounds, i.e. Aniline, 4-Chloroaniline, Toluene-2,4-diamine, 2-Naphtylamine, 4,4’-Metylenbis(2-chloroaniline), 4,4’-Metylenedianiline, N-Nitrosodiphenylamine, Benzidine, 2-Aminobiphenyl, 2-Amino-1-methyl-6-phenylimidazo[4,5-b]Pyridine, 3-Trifluoromethylaniline, p-Phenylenediamine, o-Toluidin, 4-Chloro-o-toluidin. Host molecules used in this study are Calix[4]arene and its analogs such as Azacalix[4]arene, Calix[4]carbazole, Calix[4]naphthlaene, Calix[4]pyridine, Calix[4]pyrrole, and Thiacalix[4]arene that will be denoted in this article as azacalixarene, calixcarbazole, calixnaphthalene, calixpyridine, calixpyrrole, and thiacalixarene, respectively. All host and guest molecular structures were obtained from https://pubchem.ncbi.nlm.nih.gov/ without further modification except for calixarene analogs such as azacalixarene, calixcarbazole, calixnaphthalene, thiacalixarene, which were modified from molecular structures of calixarene and then optimized by using molecular mechanics method. Toluene-2,4-diamine, 2-Amino-1-methyl-6-phenylimidazo[4,5-b] Pyridine, 2-Aminobiphenyl, 2-Naphtylamine, 3-Trifluoromethylaniline, 4,4’-Metylenedianiline, 4-Chloroaniline, 4-Chloro-o-toluidin, Aniline, Benzidine, 4,4’-Metylenbis(2-chloroaniline), N-Nitrosodiphenylamine, o-Toluidin, p-Phenylenediamine are denoted as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, respectively. Azacalixarene, calixarene, calixcarbazole, calixnaphthalene, calixpyridine, calixpyrrole, and thiacalixarene denoted are denoted as A, B, C, D, E, F, and G, respectively. A1 means inclusion complex between azacalixarene and toluene-2,4-diamine, B3 means inclusion complex between calixarene and 2-aminobiphenyl, and so on.

2.2. Molecular docking simulation
ArgusLab version 4.0.1 has been used as tool for molecular docking simulation [23], which has also been used as tool for molecular docking simulation in the previous researches [24-28]. In this molecular docking simulation, the guest molecule of aromatic amine compounds were treated as ligand and host molecule of calixarene and its analogs were treated as binding site. This molecular docking simulation used AScore scoring function, binding sitebox size for host molecule calculated by the software, with grid resolution of 0.4Å, docking engine of GA (Genetic Algorithm) Dock with flexible ligand, population size of 50, max. generation of 1000, elitism of 5, mutation rate of 0.2, and crossover rate of 0.8.

2.3. PM3 semiempiric quantum calculation
The host molecules of calixarene and its analogs, guest molecules of aromatic amine, and its inclusion complexes were calculated by using PM3 semiempiric quantum method. The calculation was carried out by using Gaussian 2009 Rev. D 01 [29] software package and computer server with specification, i.e. Intel Xeon E5 Processor (24 core processor), 32GB DDR3 RAM, and 1 TB hard disk. The binding energy value between host and guest molecule is calculated by using equation (1).

$$\Delta E = E_{\text{optimized inclusion complex}} - (E_{\text{optimized host}} + E_{\text{optimized guest}}) \tag{1}$$
Where $E_{\text{optimized inclusion complex}}$ is the energy value of optimized inclusion complex, $E_{\text{optimized host}}$ is the energy value of optimized host molecule, and $E_{\text{optimized guest}}$ is the energy value of optimized guest molecule.

3. Results and discussion

The result of PM3 semiempiric quantum calculation between aromatic amine and calixarene analogs show the different result in binding energy. It is shown in Figure 1(a), Figure 1(b), Figure 1(c), Figure 1(d), Figure 1(e), Figure 1(f), and Figure 1(g) for binding energy of azacalixarene and aromatic amine, calixarene and aromatic amine, calixcarbazole and aromatic amine, calixnaphthalene and aromatic amine, calixpyridine and aromatic amine, calixpyrrole and aromatic amine, thiacalixarene and aromatic amine, respectively.

From Figure 1(a), it is shown that all binding energy between azacalixarene and aromatic amine compounds is negative, except azacalixarene and 2-amino-1-metil-6-fenilimidazo[4,5-b]pyridine inclusion complex (A2 inclusion complex), which has binding energy value of 0.31 Hartree. This result is similar with molecular docking simulation result. It proves that this positive value is caused by the "big structure" of 2-Amino-1-metil-6-fenilimidazo[4,5-b]pyridine that does not fit in the “cavity” of azacalixarene molecule, so that it cause big steric hindrance between 2-Amino-1-metil-6-fenilimidazo[4,5-b]pyridine and azacalixarene. The negative value of binding energy means that the inclusion complex between two molecules is occurred spontaneously, and the positive value means that the inclusion complex between two molecules is not occurred spontaneously.

![Figure 1](image_url)
Figure 1(b) show that the binding energy between all of aromatic amine compounds and calixarene is negative except for B2, B4, B9, and B10 inclusion complex, which B2 has most positive value of binding energy, i.e. 0.28 Hartree. Similar with the case of A2 inclusion complex, this can be happened because the inclusion complex in B2 has biggest steric hindrance among the other three inclusion complex, B2, B4 and B9, which is caused by the guest molecule does not fit with the cavity of host molecule in B2 inclusion complex. There are seven inclusion complex between aromatic amine and calixcarbazole that have positive binding energy value. It means that calixcarbazole is the worst host molecule for aromatic amine extraction based on PM3 semiempiric quantum calculation. From Figure 1(d) and Figure 1(e), it can be concluded that all of the inclusion complex between aromatic amine compounds and host molecules (calixnaphthalene and calixpyridine respectively) is formed spontaneously because all of them have negative binding energy, with average value of -0.006 Hartree for inclusion complex between aromatic amine and calixnaphthalene, and -0.011 Hartree for inclusion complex between aromatic amine and calixpyridine.

Figure 1(f) show that the inclusion complex in F2, F7, F11, and F12 is not occurred spontaneously because they have positive binding energy value, which is 0.36 Hartree, 0.004 Hartree, 0.25 Hartree, and 0.33 Hartree, respectively. Based on Figure 1(g), all of aromatic amine compounds form inclusion complex with thiacalixarene spontaneously except 2-amino-1-metil-6-fenilimidazo[4,5-b]pyridine, 4,4'-methylenediammine, 4,4'-Metilenbis(2-kloroanilin) in G2, G6, and G11 inclusion complex, respectively, because they have positive binding energy value.

From this research, it can be concluded that calixnaphthalene and calixpyridine is the best calixarene analogs for extraction of aromatic amine compounds because all of their inclusion complexes with aromatic amine compounds have negative binding energy with the range of -10.5 kJ/mol till -26.3 kJ/mol. Song et al have reported theoretical studies of the inclusion phenomena between β-cyclodextrin and organic amines [30]. They found that the inclusion complex binding energy has the range between -15 kJ/mol and -75 kJ/mol. It can be concluded that β-cyclodextrin is better than calixnaphthalene and calixpyridine for the extraction of aromatic amine compounds. This is because β-cyclodextrin has “cavity” structure relatively bigger than the cavity structure of calixnaphthalene and calixpyridine, so that β-cyclodextrin can form more stable inclusion complex with aromatic amine compounds and its binding energy will be more negative.

4. Conclusion
From PM3 semiempiric quantum calculation, it can be concluded that the most suitable host molecule of calixarene analogs for extraction of aromatic amine compounds are Calixnaphthalene and Calixpyridine because all of aromatic amine compounds form inclusion complex with them spontaneously shown by negative value of binding energy. However, this PM3 semiempiric quantum calculation result must be validated by using higher and better theory level of computational method, such as DFT (Density Functional Theory), in order to get more accurate results.

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References
[1] Sax N I 1986 Cancer Causing Chemicals (Van Nostrand Reinhold) 457
[2] Scott T N 1962 Carcinogenic & Chronic Hazards of Aromatic Amines (Amsterdem: Elsevier)
[3] Feber K H 1978 Encyclopedia of Chemical Technology (New York: Wiley)
[4] Seiler J P 1977 Mutat. Res. 58 353
[5] Kirk O 1978 Encyclopedia of Chemical Technology (New York: Wiley)
[6] Desai M N and Patel R P 1972 Anti-Corros. Method. Mater. 19 2
[7] Erdemir S, Bahadir M and Yilmaz M 2009 J. Haz. Mat. 168 1170
[8] Asfari Z, Hmer V B, Harrowfield M M and Vicens M J 2001 Calixarenes (Dordrecht: Kluwer Academic)
[9] Crini G and Peindy H N 2006 *Dyes Pigm.* **70** 204
[10] Delval F, Crini G, Morin N, Vebrel J, Bertini S and Torri G 2002 *Dyes Pigm.* **53** 79
[11] Janus L, Crini G, El-Rezzi V, Morcellet M, Cambiaghi A, Torri G, Naggi A and Vecchi C 1999 *React. Funct. Polym.* **42** 173
[12] Crini G 2003 *Bioresource Technol.* **90** 193
[13] Crini G and Morcellet M 2002 *J. Sep. Sci.* **25** 789
[14] Vicens J and Bohmer V 1999 *Calixarenes: A Versatile Class of Macrocyclic Compounds* *Topics in Inclusion Science* (Dordrecht : Kluwer Academic)
[15] Roundhill D M 1995 *Metal-complexes of calixarenes,* *Prog. Inorg. Chem.* **43** 533
[16] Gutsche C D 1998 *Calixarenes Revisited* (Cambridge: The Royal Society of Chemistry)
[17] Gale P A, Sessler J L and Kral V 1998 *Chem. Comm.* **11**
[18] Kral V, Gale P A, Jr P A, Jursikova Jr K, Lynch V and Sessler J L 1998 *Chem. Comm.* **19**
[19] Lhotak P 2004 *Eur. J. Org. Chem.* **8** 1675
[20] Wang M-X 2012 *Acc. Chem. Res.* **45** 182
[21] Yang P, Jian Y, Zhou X, Li G, Deng T, Shen H, Yang Z and Tian Z 2016 *J. Org. Chem.* **81** 2974
[22] Georghiou P E, Li Z, Ashram M, Chowdhury S, Mizyed S, Tran A H, Al-Saraierh H and Miller D O 2005 *Synlett.* **6** 879
[23] Thompson M A 2004 *Arguslab 401* (Planaria Software LLC)
[24] Setiadji S, Sundari C D D, Nuryadiad W, Zayyinunnisya H, Cahyandari R and Ivansyah A L 2018 *Journal of Physics: Conference Series* **1090** 1 012055
[25] Nurhidayah E S, Ivansyah A L, Martoprawiro M A and Zulfikar M A 2018 *Journal of Physics: Conference Series* **1013** 1 012203
[26] Setiadji S, Sundari C D D, Ramdhani M A, Umam A B K and Ivansyah A L 2018 *IOP Conference Series: Materials Science and Engineering* **288** 1 012138
[27] Ivansyah A L, Nurhidayah E S, Sundari C D D, Martoprawiro M A and Buchari 2019 *Journal of Physics: Conference Series* **1402** 5 055068
[28] Ivansyah A L, Martoprawiro M A and Buchari 2017 *Journal of Physics: Conference Series* **812** 1 012070
[29] Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Scalmani G, Barone V, Mennucci B, Petersson G A, Nakatsuji H, Caricato M, Li X, Hratchian H P, Izmaylov A F, Bloino J, Zheng G, Sonnenberg J L, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery J A, Jr, Peralta J E, Ogliaro F, Bearpark M, Heyd J J, Brothers E, Kudin K N, Staroverov V N, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant J C, Iyengar S S, Tomasi J, Cossi M, Rega N, Millam J M, Klene M, Knox J E, Cross J B, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann R E, Yazyev O, Austin A J, Cammi R, Pomelli C, Ochterski J W, Martin R L, Morokuma K, Zakrzewski V G, Voth G A, Salvador P, Dannenberg J J, Dapprich S, Daniels A D, Farkas Ö, Foresman J B, Ortiz J V, Cioslowski J and Fox D J 2009 *Gaussian 09, Revision D.01* (Wallingford CT: Gaussian, Inc.)
[30] Song L X, Wang H-M, Teng C F, Bai L, Xu P and Guo X-Q 2008 *Chinese Journal of Chemistry* **26** 1702