Molecular docking study of inclusion complex between aromatic amine and Calixarene analogs

A L Ivansyah1,2,*

1 Master Program in Computational Science, Faculty of Mathematics and Natural Sciences, Institut Teknologi Bandung, Jl. Ganesha No. 10, Bandung, Indonesia
2 Analytical Chemistry Research Group, Department of Chemistry, Faculty of Mathematics and Natural Sciences, Institut Teknologi Bandung, Jl. Ganesha No. 10, Bandung, Indonesia

*atthar@compscience.itb.ac.id

Abstract. A molecular docking was performed in this research by using ArgusLab version 4.0.1. It was used to explore the capability of Calixarene analogs for aromatic amine extraction. There are 6 Calixarene analogs used in this research, i.e. Calixpyrrole, Calixpyridine, Thiacalixarene, Heterocalixaromatic, Calixcarbazole and Calixnaphthalene; and the aromatic amine used in this research are Aniline, 4-Chloroaniline, Toluene-2,4-diamine, 4,4'-Methylendibis(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. 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 with grid size of 0.4 Å, GA docking engine with flexible ligand, 50 population sizes, 1000 max generations, 5 elitisms, 0.2 mutation rate, and 0.8 crossover rate. Calixcarbazole and Calixnaphthelene is the best host molecule for aromatic amines extraction because the inclusion complexes formed between them have 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. Thus, it is necessary to develop a material that can extract this waste very well. One type of material that can be used is supramolecular material. In this research, computational investigation has been carried out by using molecular docking simulation 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 two sections. First, construct the host and guest molecule, and the second is molecular docking simulation.
2.1. Construct the host and guest molecule

Guest molecules used in this research are 14 aromatic amine compounds, i.e. Aniline, 4-Chloroaniline, Toluene-2,4-diamine, 2-Naphtylamine, 4,4’-Methylenebis(2-chloroaniline), 4,4’-Methylenebridianiline, N-Nitrosodiphenylamine, Benzidine, 2-Aminobiphenyl, 2-Amino-1-methyl-6-phenylimidazo[4,5-b]Pyridine, 3-Trifluoromethylanine, p-Phenylendiamine, 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]naphthlene, Calix[4]pyrrole, Calix[4]pyrrole, and Thiocalix[4]arene, 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, calixpyrrole, calixpyrrole, and thiocalixarene, respectively. A positive value means that the inclusion complex between two molecules is occurred spontaneously, and the positive value is caused by the "big structure" of azacalixarene molecule, so that it cause big steric hindrance between inclusion complex (A2 inclusion complex), which has binding energy value of 6.83 kcal/mol. This positive value is caused by the "big structure" of 2-Amino-1-methyl-6-phenylimidazo[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-methyl-6-phenylimidazo[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.

2.2. Molecular docking simulation

ArgusLab version 4.0.1 [7] has been used as tool for molecular docking simulation, which has also been used as tool for molecular docking simulation in the previous research [8-12]. 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.

3. Results and discussion

The result of molecular docking simulation 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, calixpyrrole and aromatic amine, thiocalixarene 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-fenylimidazo[4,5-b] pyridine inclusion complex (A2 inclusion complex), which has binding energy value of 6.83 kcal/mol. This positive value is caused by the "big structure" of 2-Amino-1-metil-6-fenimidazo[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-fenimidazo[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. Binding energy of (a) Azacalixarene, (b) Calixarene, (c) Calixcarbazole, (d) Calixnaphthalene, (e) Calixpyridine, (f) Calixpyrrole, (g) Thiocalixarene and aromatic amine inclusion complex from molecular docking simulation.
Figure 1(b) show that the binding energy between all of aromatic amine compounds and calixarene is negative except for B2, B3, and B10 inclusion complex, which B10 has most positive value of binding energy, i.e. 13.85 kcal/mol. Similar with the case of A2 inclusion complex, this can be happened because the inclusion complex in B10 has biggest steric hindrance among the other two inclusion complex, B2 and B3, which is caused by the guest molecule does not fit with the cavity of host molecule in B10 inclusion complex. From Figure 1(c), it can be concluded that all of the inclusion complex between aromatic amine compounds and calixcarbazole is formed spontaneously because all of them have negative binding energy, with average value of -4.1 kcal/mol.

All of the binding energy value of inclusion complex between calixnaphthalene and aromatic amine compounds is negative, as shown in Figure 1(d). It means that the inclusion complex between calixnaphthalene and aromatic amine compounds is occurred spontaneously, similar with the inclusion complex between calixcarbazole and aromatic amine compounds. It can be occurred because the host molecule of calixcarbazole and calixnaphthalene have similar structure that can give more space for the guest molecule of aromatic amine compounds. Each of them has four moieties of carbazole and naphthalene, however two moieties have different position with the others two, as shown in Figure 2, so that the guest molecule of aromatic amine compounds will be fit in the “cavity” of host molecule.

Figure 1(e) show that the inclusion complex in E2 and E11 is not occurred spontaneously because they have positive binding energy value, which is 11.94 kcal/mol and 7.28 kcal/mol, respectively. Based on Figure 1(f), all of aromatic amine compounds form inclusion complex with calixpyrrole spontaneously except 4,4’-Metilenbis(2-kloroanilin) in F11 inclusion complex because it has positive binding energy value, i.e. 1.51 kcal/mol. All of aromatic amine compounds form inclusion complex with thiacalixarene spontaneously, except 4,4’-Methyleneedianiline in G6 inclusion complex because it has positive binding energy value, i.e. 2.77 kcal/mol, as shown in Figure 1(g).

Figure 2. The molecular structure of (a) Calixcarbazole and (b) Calixnaphthalene.

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

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