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ORIGINAL ARTICLE

Hydrogen bonding nature between calix[6]arene and piperidine/triethylamine

Sunwoo Kang · Sang Joo Lee · Shihai Yan · Kye Chun Nam · Jin Yong Lee

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Abstract We investigated the binding nature of the 1,2,3-alternate calix[6]arene with one piperidine, two piperidines, and two triethyl amines with a special emphasis on the hydrogen bonding networks by density functional theory calculations. The 1,2,3-alternate calix[6]arene strongly binds with piperidines and triethylamines at two different binding sites, exo and endo sites. In the two binding sites, the hydrogen bonding nature shows a characteristic difference. In the exo site, there formed only one hydrogen bond, while in the endo site, two hydrogen bonds except for the triethylamine. The proton transfer within the hydrogen bonding and the hydrogen bonding types, normal hydrogen bonding (NHB), short strong hydrogen bond (SSHB), and low barrier hydrogen bonding (LBHB), will be discussed in detail.

Keywords Molecular recognition · Calix[6]arene · Piperidine · Proton transfer · Hydrogen bonding · Potential surface

S. Kang · S. Yan · J. Y. Lee (✉)
Department of Chemistry, Sungkyunkwan University, Suwon 440-746, Korea
e-mail: jinylee@skku.edu
URL: http://chem.skku.ac.kr/~jinylee

S. J. Lee
Department of Infrastructure Technology Development, Supercomputing Center, 335 Gwahangno, Yuseong-gu, Daejun 305-806, Korea

K. C. Nam
Department of Chemistry, Chonnam National University, Gwangju 500-757, Korea
e-mail: kcnam@chonnam.ac.kr
URL: http://altair.chonnam.ac.kr/~chem/organic/main.htm

Abbreviations

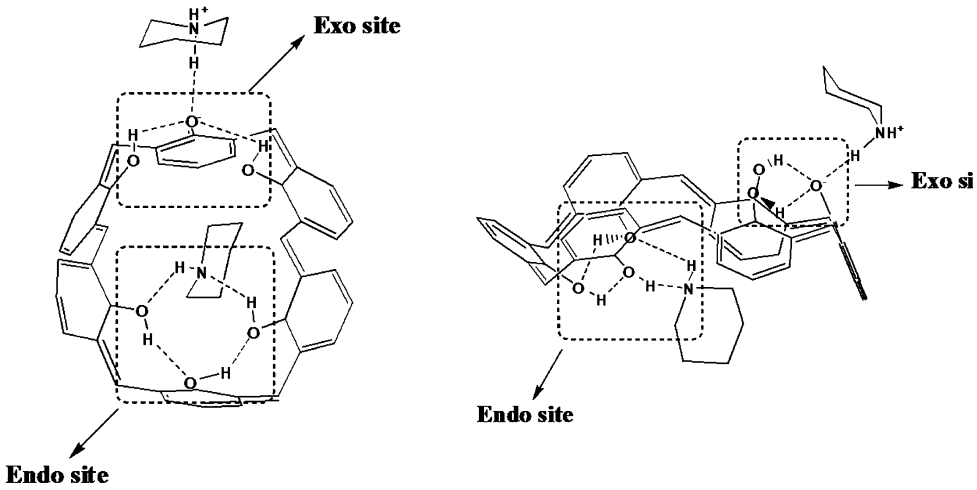
SSHB	Short strong hydrogen bonding
LBHB	Low barrier hydrogen bonding
H-bond	Hydrogen bond

Introduction

Molecular recognition is central areas of biology and chemistry, including cell adhesion, signal transduction, enzyme inhibition, and catalysis [1–3]. Obviously, to develop a new host molecular family that binds a specific guest species very selectively is an essential goal in molecular recognition. For selective host-guest binding, various types of intermolecular interactions have been utilized such as hydrogen bonding, cation-π interaction, and X–H… anion interactions [4].

Among the host families developed until now, calix[*n*]arenes have been widely used very efficiently, in particular, calix[4]arenes [5–7]. However, as the number of arenes (*n*) increases it becomes more difficult to synthesize calix[*n*]arene due to the more complicated structural features. After the first synthesis of calix[6]arene [8, 9], a number of its derivatives have been published to report the selective guest species [10–13]. Ammonium ions play an important role in biological and chemical processes [10–13] as well as in the medical science [14–16], thus it is highly demanding to design and synthesize an amine selective host molecules. In this context, there have been a number of studies on the interactions between calixarenes and amines since the first report by Bauer and Gutsche [17], ranging from the thermodynamic and electrochemical aspects [18–20] to the structures and binding modes [21].

Scheme 1 Hydrogen bonding modes in the endo- and exo-complexes between calix[6]arene and piperidine



Top view Side view

In particular, it was reported that the calix[6]arene could be doubly deprotonated by aliphatic amines, and the second proton transfer can be affected by the types of amines [22].

Recently, one of us and coworkers reported the structural features and Endo/Exo complexes between calix[6]arene and amines [23]. They found, from the NMR and X-ray structural analysis, that the calix[6]arene exists as 1,2,3-alternate conformation and binds with two piperidines through the hydrogen bondings. Interestingly, they further observed in the complex the calix[6]arene dianion and the piperidinum ion. However, the detailed hydrogen bonding nature was not clarified yet. For example, what is the difference between the H-bonds in exo-calix and endo-calix (See the Scheme 1 for notation)? How easily does the proton transfer in both the H-bonds? What is the strength of both the H-bonds? Here, we report the characteristic feature of the hydrogen bondings in the complexes of the calix[6]arene with one or two piperidines and compare with that in the complex of the calix[6]arene with two triethylamines.

Calculational methods

All of the geometry structures were carried out the density functional theory (DFT) calculations using the nonlocal density function of Becke's three parameters employing Lee-Yang-Parr functional (B3LYP) with 6-31G** basis set implemented in the Gaussian 03 programs [24]. For the geometry optimization of 1,2,3-alternate calix[6]arene and its complexes with one piperidien, two piperidines, and two triethylamines, the X-ray structures were used as trial structures. To compare the H-bonding nature in the exo-calix and endo-calix, we obtained the potential energy surfaces for the proton transfer in H-bondings in the exo and endo binding sites for all the complexes investigated. For the potential energy surface (PES), the hybrid-meta GGA method [25], namely (MPWB1K), was employed with 6-31G** basis sets.

Results and discussion

Complex between calix[6]arene and one piperidine

Figure 1a shows the calculated structure of the 1,2,3-alternate calix[6]arene, and Fig. 1b, c show the hydrogen bonding features by structural parameters in the exo and endo sites, respectively. As seen in Fig. 1b, c, the calix[6]arene has similar cyclic H-bonding networks in the two binding sites as noted in the O···O distances, 2.673, 2.714, and 2.940 Å at the exo site, and 2.666, 2.713, and 2.963 Å at the endo site.

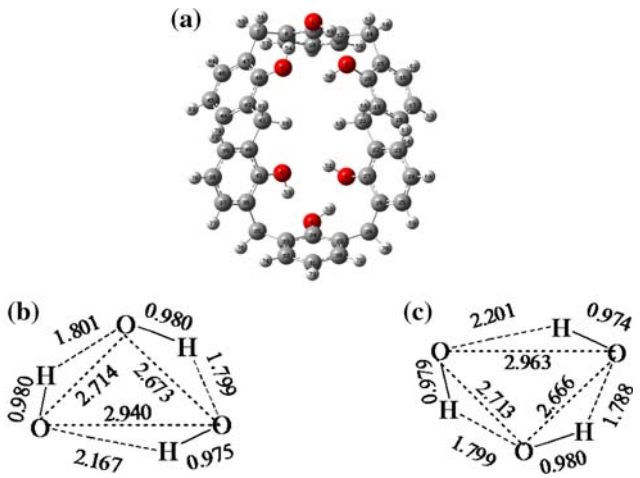


Fig. 1 The calculated structure of the calix[6]arene (**a**), and the hydrogen bonding networks in the exo site (**b**) and the endo site (**c**)

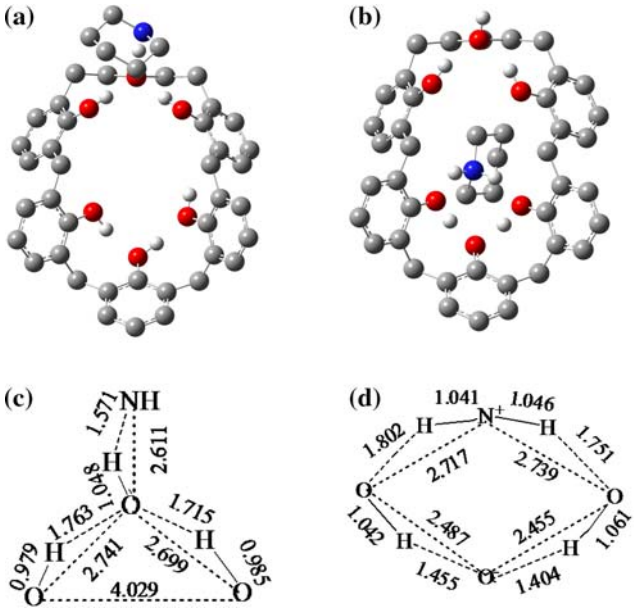


Fig. 2 The calculated structures of the complexes between the calix[6]arene and the one piperidine at the exo site (**a**) and the endo site (**b**), and the hydrogen bonding networks in the exo site (**c**) and the endo site (**d**)

Figure 2a, b show the calculated structures of the complexes between calix[6]arene and one piperidine in the exo and endo sites, respectively. When the piperidine interacts with the calix[6]arene, there is only one H-bond between the piperidine and the calix[6]arene at the exo binding site, while two H-bonds at the endo binding sites. As seen in Fig. 2c, d, in the exo complex, the proton transferred completely from the oxygen atom that directly interacting with piperidine, resulting in negative charge at the oxygen, which is consistent with the previous experiment [23]. In particular, the H-bond must be very strong due to the short O···N distance of 2.548 Å. Thus, this H-bond can be considered as short strong hydrogen bonding (SSHB) that is often found in enzymatic systems and charged systems [26–29]. The negatively charged oxygen due to the proton transfer makes the two H-bonds stronger than those in the host. This can be seen from the reduced O···O distances. The O···O distances in the two H-bonds between the cyclic hydroxyl groups are 2.620 and 2.651 Å, which were much reduced from the 2.673 and 2.714 Å in the host. On the other hand, in the endo complex, the proton transferred from the oxygen that is not directly interacting with the piperidine, thus the two H-bonds between the piperidine and the calix[6]arene can be considered as normal H-bonds with the N···O distances of 2.717 and 2.739 Å. However, the O···O distances in the two H-bonds between the cyclic hydroxyl groups are 2.487 and 2.455 Å, which were much reduced from the 2.666 and 2.713 Å. The interaction energies of the exo and endo complexes are 11.90 and 10.52 kcal/mol, respectively.

Figure 3 shows the potential energy surfaces for the proton transfer between the nitrogen atom of the piperidine and the oxygen atom at the exo (O_{exo}) and the endo (O_{endo}) sites for the complex of calix[6]arene and one piperidine. It is very interesting to note that the barrier for the proton transfer seems to be very low in the exo complex, which can be considered as low barrier hydrogen bond (LBHB) though the proton transferred state is slightly lower in energy [30–33]. Thus, the proton nontransferred structure may be allowed in a certain environment. Very differently, in the endo complex, the potential surface shows that the proton transferred completely from the oxygen to the nitrogen without barrier, and the proton nontransferred structure apparently may not be allowed due to the steep potential difference of ca. 36.26 kcal/mol.

Complex between calix[6]arene and two piperidines

Figure 4a shows the calculated structure at different angle of view for the complex between calix[6]arene and two piperidines where one piperidine binds at the exo site and one at the endo site. There is only one hydrogen bonding at the exo site, while two hydrogen bondings at the endo site. Differently from the complex with one piperidine, the proton was not transferred to the piperidine in both the exo

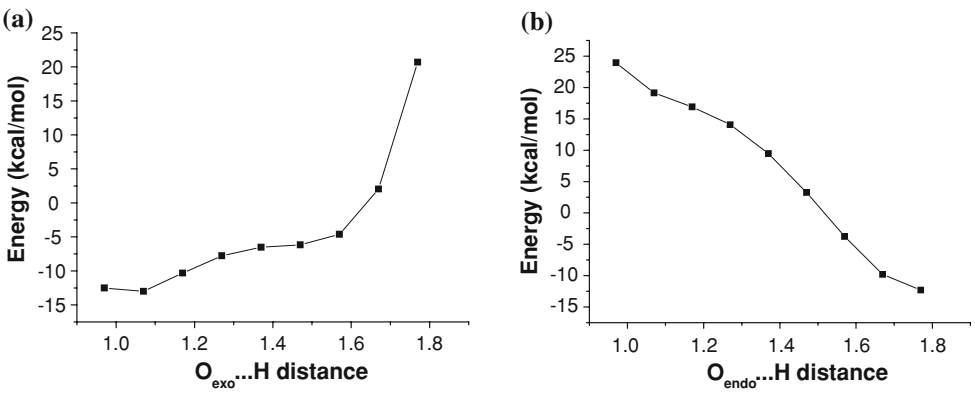


Fig. 3 Potential energy surfaces for the proton transfer between the nitrogen atom of the piperidine and the oxygen atom at the exo, O_{exo}, (**a**) and the endo site, O_{endo}, (**b**) for the complex of calix[6]arene and one piperidine

and endo binding sites. The bond length of O_{exo}–H increased slightly due to the stronger interaction between nitrogen atom of the piperidine and hydrogen of calix[6]-arene. In the exo binding site, the distance of N···H and N···O was calculated to be 1.580 and 2.621 Å, respectively. In addition, the calculated O···O distances in the other two H-bonds between the cyclic hydroxyl groups are 2.721 and 2.689 Å, which were quite similar to the O···O distances of 2.714 and 2.673 Å in the host. Thus, the H-bond at the exo site can be considered as a normal H-bond. In the endo binding site, the H-bonds between the nitrogen atom of the piperidine and O_{endo} can also be considered as a normal H-bond because the N···O distances are 2.701 and 3.056 Å, respectively, and cannot be considered as SSHB. The O···O distances in the other two H-bonds between the cyclic hydroxyl groups are 2.718 and 2.629 Å, respectively, which are quite similar to those in calix[6]arene.

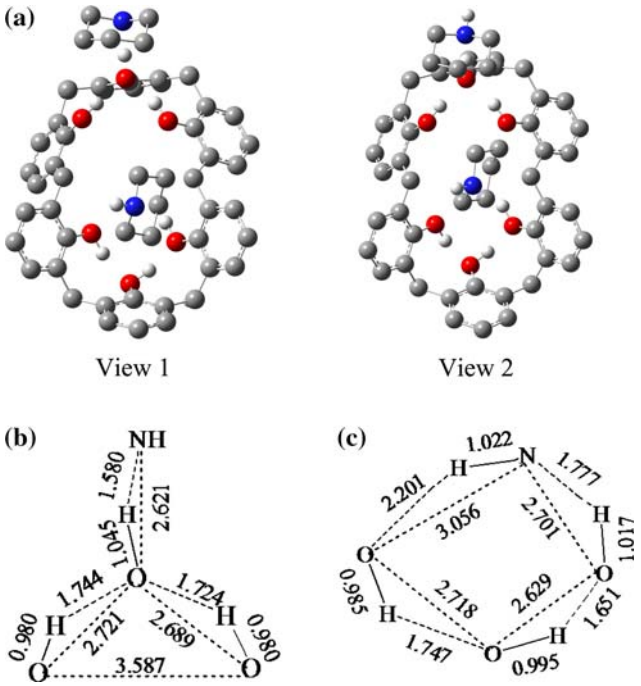


Fig. 4 The calculated structure of the complex between the calix[6]arene and two piperidines (**a**), and the hydrogen bonding networks in the exo site (**b**) and the endo site (**c**)

Figure 5 shows the potential energy surfaces for the proton transfer between the nitrogen atom of the piperidine and the oxygen atom at the exo (O_{exo}) and the endo (O_{endo}) sites for the complex of calix[6]arene and two piperidines. In both the exo and endo binding sites, the potential surfaces show that the proton transfer does not take place, and the proton transferred structures are unstable and must go back to the proton nontransferred structure without barrier. Furthermore, the proton transferred structure apparently may not be allowed due to the steep potential differences of ca. 1.39 and 8.93 kcal/mol for the exo and the endo site, respectively.

Complex between calix[6]arene and two triethylamines

Figure 6a shows the calculated structure at different angle of view for the complex between calix[6]arene and two triethylamines where one triethylamine binds at the exo site and one at the endo site. In the exo binding site, the hydrogen bonding structure was quite similar with the complex between the calix[6]arene and two piperidines. In the exo site, the distances of N···H and O···N were calculated to be 1.600, 2.637 Å, respectively, which are slightly longer than those in the exo site of the complex between the calix[6]arene and two piperidines. Based on the distances, all the H-bonds can be considered as normal hydrogen bonding. In the endo site, the hydrogen bonding network is remarkably different from that of the complexes between the calix[6]arene and piperidines. Only one H-bond is formed between the nitrogen atom of triethylamine and one of the hydroxyl group of the calix[6]arene, while there are two H-bonds between the piperidine and the calix[6]arene. The H-bond between the triethylamine and the host can be considered as normal H-bonds due to the N···O distance of 2.653 Å. In addition, the O···O distances between the hydroxyl groups were calculated to be 2.592

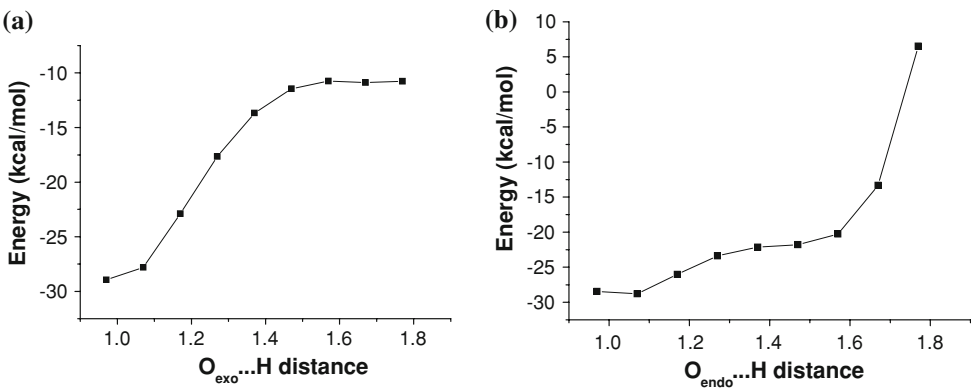


Fig. 5 Potential energy surfaces for the proton transfer between the nitrogen atom of the piperidine and the oxygen atom at the exo, O_{exo}, (**a**) and the endo site, O_{endo}, (**b**) for the complex of calix[6]arene and two piperidines

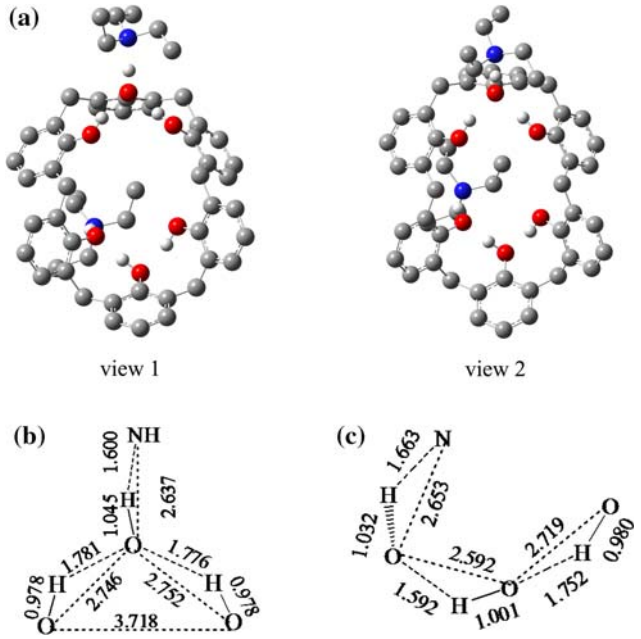


Fig. 6 The calculated structure of the complex between the calix[6]arene and two triethylamines (**a**), and the hydrogen bonding networks in the exo site (**b**) and the endo site (**c**)

and 2.719 Å, which were quite similar to the other complexes and the host molecule.

Figure 7 shows the potential energy surfaces for the proton transfer between the nitrogen atom of the triethylamine and the oxygen atom at the exo (O_{exo}) and the endo (O_{endo}) sites for the complex of calix[6]arene and two triethylamines. Differently from the complex with two piperidines, in this complex, in both of the exo and endo binding sites, the proton transferred structures are in the potential energy minima. Nevertheless, the potential surfaces show that the proton nontransferred structure is more stable than the proton transferred one by about 5.67 and 9.56 kcal/mol in the exo and endo sites, respectively. In particular, in the exo binding site, the potential energy barrier for the proton transfer between the nitrogen and the oxygen atoms seems to be not that high, ~6.10 kcal/mol. Thus, this H-bond may be considered as LBHB depending on the environment. However, the proton transfer may not take place in the endo binding site because of the relatively high potential barrier of ~8.79 kcal/mol.

Conclusion

The 1,2,3-alternate calix[6]arene strongly binds with piperidines and triethylamines at two different binding sites, exo and endo sites. In the host compound, in both the exo and endo sites, there are three cyclic H-bonds between the three OH groups. In binding with one piperidine at the exo site, one H-bond is formed with proton transfer from OH to the nitrogen of piperidine and the H-bond can be characterized as LBHB because of low barrier and flat potential energy surface for the proton transfer. In binding with one piperidine at the endo site, two H-bonds are formed with proton transfer from OH to the nitrogen of piperidine but these two H-bonds can be characterized as normal H-bonds. In both the exo and endo site binding, the H-bonds between the hydroxyl groups are considered as SSHB due to the very short O···O distances that are much shortened from the host compound. In binding with two piperidines, the H-bonding network showed a significant difference from the complexes with one piperidine. The proton transfer takes place only in the endo binding site, and H-bonds between the hydroxyl groups are not considered as SSHB due to the increased O···O distances. In binding with two triethylamines, the binding feature is similar to the complex with two piperidines except that, in the endo site binding, there is only one H-bond between the hydroxyl group and the amine.

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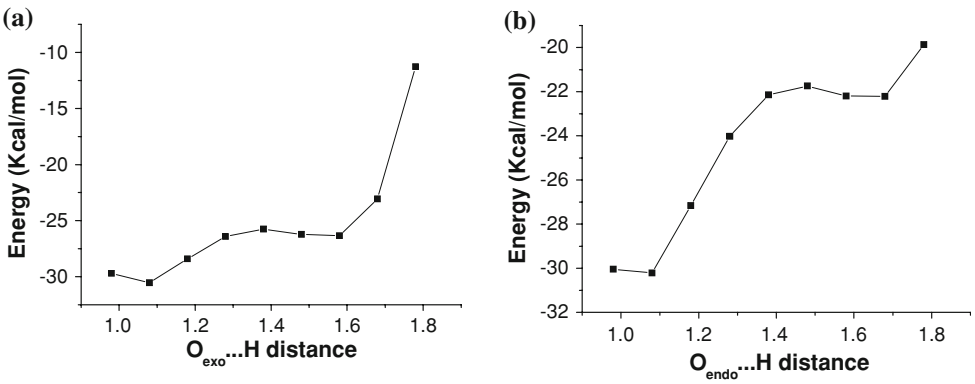

Fig. 7 Potential energy surfaces for the proton transfer between the nitrogen atom of the triethylamine and the oxygen atom at the exo, O_{exo}, (**a**) and the endo site, O_{endo}, (**b**) in the complex of calix[6]arene and two triethylamines

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