

Elucidating the mechanism of binding of chromate to cucurbit[6]uril: a DFT study

Mahesh Sundararajan · Swapan K. Ghosh

Received: 6 May 2011 / Accepted: 19 June 2011 / Published online: 8 July 2011
© Springer Science+Business Media B.V. 2011

Abstract We report the binding of chromate, a toxic heavy metal ion to the macrocyclic host molecule, cucurbituril using density functional theory. Due to the anionic nature of the guest molecule and the portals of the host molecule, we propose that the binding mechanism should be assisted by cations. The calculated barrier for chromate binding to cucurbituril is found to be ~ 17 kcal mol⁻¹. The large barrier can be attributed to portal opening of the host molecule, electrostatic repulsion between the guest molecule and the portals of the host molecule and the solvent re-organization around guest molecule.

Keywords Chromate · Cucurbituril · Density functional theory · Binding affinity · Solvation and mechanism

Introduction

Toxic heavy metals present a worldwide environmental pollution problem. One of the most common polluting metals is chromium arising as a by-product of many industrial and military processes, including the manufacture of nuclear weapons. The oxidized form of chromium (Cr(VI)) is toxic and soluble, whereas Cr(III) is much less toxic and tends to form insoluble hydroxides. Indeed, Cr(VI) compounds are among the 88 recognized (class I) human carcinogens, whilst Cr(III) is regarded as an

essential micronutrient [1]. Reduction of Cr(VI) to Cr(III) is thus a potentially useful process for the remediation of chromium contamination [2]. Certain bacteria containing cytochrome *c*₇ type protein have the ability to immobilize the metal ion via electron transfer reduction process [3]. There is thus considerable activity towards promoting measures which can increase the effectiveness of such bioremediation of metal contamination.

Chemists are particularly interested to design molecules suitable for binding toxic metal ions such as chromate. In fact, Behrend et al. [4] was the first to notice that addition products of potassium chromate and macrocyclic host molecule. This macrocyclic host molecule has been later known as Cucurbituril (CB), whose X-ray crystal structure was reported by Freeman et al. [5]. CBs are specially designed to bind cations over anions which are largely governed by ion–dipole interactions. CBs have the ability to bind variety of molecules including neutral [6, 7], cationic [8, 9] and anionic molecules [10, 11]. However, anions binding to CBs are somewhat rare. X-ray crystal structure of chloride anion encapsulated inside CB-[5] is reported [10]. Here the halide anion is supported by a potassium ion or a lanthanide ion [11] which seal the portal of CB-[5].

On the computational side, calculations were somewhat restrained due to the size of the host molecule. Pichierri [12, 13] pinpointed the large stabilities of native and thio-derivatives of CBs based on the gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) using density functional theory (DFT) based calculations. Gejji and co-workers [14, 15] used DFT to understand the binding behaviour of ferrocene in CB-[6] by computing the NMR chemical shifts for different conformers of ferrocene and for other molecules. The binding preference of anti-cancer

M. Sundararajan · S. K. Ghosh (✉)
Theoretical Chemistry Section, Bhabha Atomic Research Centre,
400 085 Mumbai, India
e-mail: skghosh@barc.gov.in

S. K. Ghosh
Homi Bhabha National Institute, 400 094 Mumbai, India

metal complex (oxaliplatin) to CBs were also studied recently [16].

Due to the toxic nature of chromate di-anion (CrO_4^{2-}), possible ways to separate it out from the natural environment is necessary. We propose a mechanism of CrO_4^{2-} binding to CB-[6] using DFT based calculations.

Computational details

We have used BP86 functional in conjunction with medium sized basis set (def2-SV(P)) for geometry optimizations. For energetics, the B3LYP functional with TZVP (triple zeta quality) was employed. It has been known in the past that such an approach saves computational time as geometries are less sensitive to change in larger basis sets, but the corresponding energies are significantly influenced by large basis set [17]. To speed up the calculations, a resolution of identity (RI) approximation is invoked as implemented in TURBOMOLE [18] by using def2-SV(P) auxiliary basis for Coulomb exchange terms. No such approximations have been used for the energy evaluation with TZVP basis set. The binding energies are calculated as per equations in Table 1. Further, in Table 1, the six water molecules which formed part of the product in some cases are not the individual six water molecules, but they form a cyclic planar hydrogen bonded complex. Bryantsev et al. [19] reported the formation of cyclic hydrogen bonded network of six water molecules with the binding energy of $50.7 \text{ kcal mol}^{-1}$ using B3LYP functional in conjunction with large basis sets. Our calculated value (B3LYP/TZVP//BP86/def2-SV(P)) $48.8 \text{ kcal mol}^{-1}$ is also close to the value reported by Bryantsev et al. [19].

Results and discussion

Structure of bare host and solvated guest molecules

Important geometric parameters of CB-[6] such as the depth (6.27 \AA), the width at the core (10.2 \AA) and at the

portals (7.3 \AA) of CB-[6] are fairly reproduced by the calculations (Fig. 1). Further, our calculated geometric parameters are consistent with the previously reported values using B3LYP functionals [16, 20]. Our calculated energy gap of 6.58 eV (HOMO-LUMO) for CB-[6] is close to the values reported in earlier calculations [16].

Due to anionic nature of CrO_4^{2-} , the HOMO of the species is unbound ($+3.92 \text{ eV}$) and hence, we have considered alternative chromate species such as protonated chromate (HCrO_4^{1-}) and solvated CrO_4^{2-} (Fig. 1). As noticed earlier, the proton affinity of CrO_4^{2-} is larger than that of the hydration free energy of the proton and hence at physiological pH, a protonated chromate might be expected [17].

We have solvated the CrO_4^{2-} with six water molecules, whose optimized solvated structure is similar to that of the experimentally observed sulfate di-anion [21]. Three water molecules are hydrogen bonded (1.98 \AA) to the apical oxygen of CrO_4^{2-} , whereas three other water molecules are anchoring the equatorial oxygens of CrO_4^{2-} via hydrogen bonding (1.84 \AA). For this solvated structure, the HOMO is bound state (-0.39 eV) due to the solvation of negative charges by six water molecules. In fact, we have found that about 0.35 e^- of charges are reduced by the water molecules as compared to the bare chromate due to the incorporation of explicit solvent molecules.

(a) Solvated CrO_4^{2-} binding to CB-[6]

We have considered two different binding motifs of solvated CrO_4^{2-} to CB-[6] which differ by the number of water molecules hydrogen bonded to CB-[6] (Fig. 2). In the first structure, the water molecules and the CrO_4^{2-} are encapsulated by CB-[6] (Fig. 2a). In the second structure, the water molecules are hydrogen bonded to the CB-[6] portals which further anchor the CrO_4^{2-} molecule (Fig. 2b). However, formation of CrO_4^{2-} adduct with CB-[6] is unfavorable in both the cases. The first structure is energetically unfavorable by $101 \text{ kcal mol}^{-1}$, whereas the second structure is unfavorable by 15 kcal mol^{-1} . When both water molecules and CrO_4^{2-} are inside CB-[6], we note that CB-[6] host molecule needs to undergo large portal opening. However, in the second structure, no such severe geometric distortion of the host molecule is necessary. Hence, the calculated relaxation energy of the host molecule for the first and second structures are ~ 41 and $9.8 \text{ kcal mol}^{-1}$. However, both modes of binding do not lead to favorable binding energies with CB-[6] and hence alternative binding motifs need to be considered.

Table 1 Computed binding energies (BE), kcal mol^{-1}

Reaction	BE
$\text{CB-[6]} + \text{HCrO}_4^{1-} \rightarrow \text{CB-[6]-HCrO}_4^{1-}$	+1.3
$\text{CB-[6]} + \text{CrO}_4^{2-} \cdot 6(\text{H}_2\text{O}) \rightarrow \text{CB-[6]-CrO}_4^{2-} \cdot 6(\text{H}_2\text{O})$	+14.8
$\text{CB-[6]} + \text{K}^+(\text{H}_2\text{O})_6 \rightarrow \text{CB-[6]-K}^+ + (\text{H}_2\text{O})_6$	-43.3
$\text{CB-[6]-K}^+ + \text{CrO}_4^{2-} \cdot 6(\text{H}_2\text{O}) \rightarrow \text{CB-[6]-K}^+ \cdot \text{CrO}_4^{2-} \cdot 6(\text{H}_2\text{O})$	-103.2
$\text{CB-[6]-K}^+ \cdot \text{CrO}_4^{2-} \cdot 6(\text{H}_2\text{O}) + \text{K}^+(\text{H}_2\text{O})_6 \rightarrow \text{CB-[6]-K}^+ \cdot \text{CrO}_4^{2-} \cdot 6(\text{H}_2\text{O}) \cdot \text{K}^+ + 6(\text{H}_2\text{O})$	-117.3

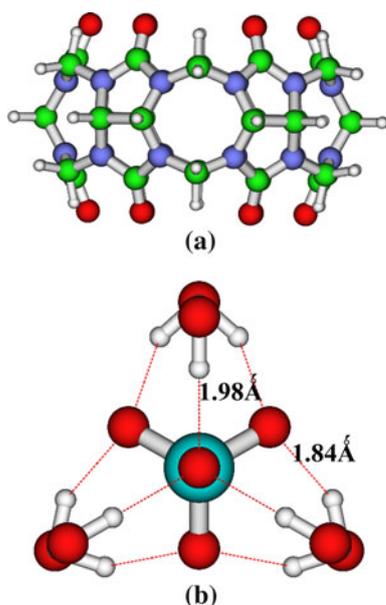


Fig. 1 Structure of (a) CB-[6] and (b) solvated chromate

(b) HCrO_4^{1-} binding to CB-[6]

As mentioned earlier, HCrO_4^{1-} exists in equilibrium with the CrO_4^{2-} species at physiological pH [17]. Due to the unfavorable binding energies of solvated CrO_4^{2-} , we have considered the binding of protonated CrO_4^{2-} to CB-[6]. In the optimized structure, the proton attached to CrO_4^{2-} oxygen is strongly hydrogen bonded (2.51 Å) to the portal oxygen of CB-[6]. The calculated binding affinity is marginally unfavorable (1.3 kcal mol⁻¹).

(c) Cation assisted CrO_4^{2-} binding to CB-[6]

We have explored alternative models such that binding for solvated CrO_4^{2-} can be energetically feasible in CB-[6]. We believe that anion encapsulation in CB-[6] is preceded by a cation binding to the portals of CB-[6] [10, 11]. In

fact, Nau and co-workers [22] proposed this to be the first step based on experimental and molecular mechanics calculations. We find that the formation of such a cation-CB-[6] is favorable by 43.1 kcal mol⁻¹ when a potassium ion is used. The six glycol-uril carbonyl groups form strong bonds with the metal ion ($\text{C}=\text{O}\cdots\text{K}^+ = 3.25$ Å) and this metalated CB-[6] is used here for binding the CrO_4^{2-} ion. Other alkali metal ions such as sodium and rubidium ions are also considered, whose $\text{C}=\text{O}\cdots\text{Na}^+ = 3.20$ Å and $\text{C}=\text{O}\cdots\text{Rb}^+ = 3.29$ Å, respectively. The cation binding affinity of CB-[6] increases with increasing ionic radius of the metal ions. As the ionic radii of the metal ion increases, the oxygen at the portals of CB-[6] can strongly interact with larger size ion (rubidium ion) as compared to the smaller sized ion (sodium). In the forthcoming section, we will discuss the mechanism of solvated CrO_4^{2-} binding to potassium bound CB-[6].

We have carried out a series of constrained geometry optimization with varying $\text{K}^+-\text{CrO}_4^{2-}$ bond lengths (Fig. 3). We have brought the solvated chromate from 25 Å (with respect to K^+ ion bound to one end of the portals of CB-[6]), to 15 Å at one incremental distances (20 Å). From, 15 Å, we have gradually decreased the $\text{K}^+-\text{CrO}_4^{2-}$ distance by one unit until 4 Å.

From 25 to 10 Å, we find that no severe geometric change takes place both at CrO_4^{2-} centre and at the CB-[6] portals. However, due to the presence of potassium at the portal of CB-[6], the binding of CrO_4^{2-} to CB-[6] is energetically favorable which is largely driven by electrostatic interactions. The CrO_4^{2-} binding affinity increases from 20 (at 25 Å) to 34 kcal mol⁻¹ (at 10 Å) upon decreasing the $\text{K}^+-\text{CrO}_4^{2-}$ distance. However, for the change in K–Cr distance from 9 to 7 Å, the binding affinity is found to decrease as compared to the 10 Å structure due to the electrostatic repulsion between the CrO_4^{2-} and the portals of CB-[6] molecule. The optimized structure at 9–7 Å clearly shows that water molecules hydrogen bonded to CrO_4^{2-} start becoming desolvated. Of the three structures, the 7 Å structure of CrO_4^{2-} is the most

Fig. 2 Optimized structures of solvated chromate with CB-[6]. a Encapsulated. b Peripheral

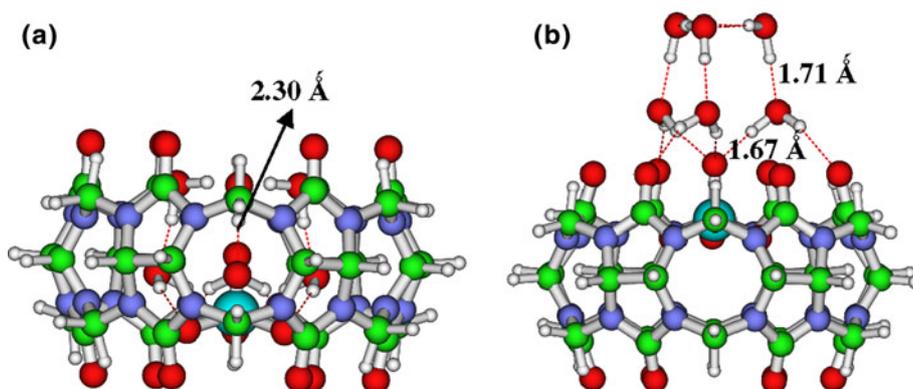
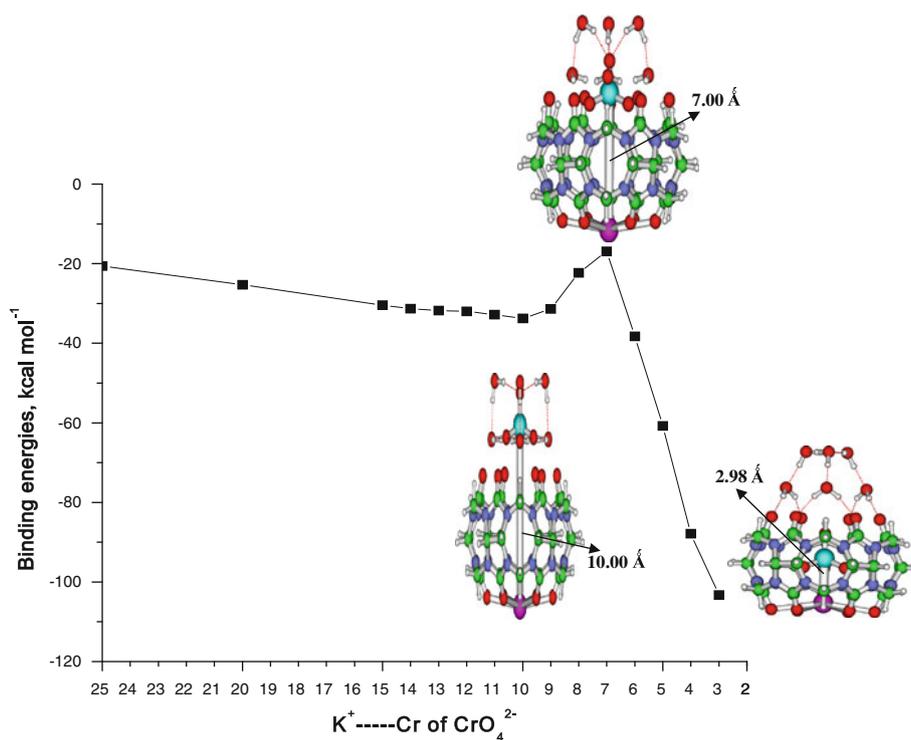


Fig. 3 Potential energy surface for chromate binding to CB-[6]



desolvated (Fig. 3), and the water molecules are now found to form hydrogen bonds with CB-[6] portal oxygens. For this structure, the CrO_4^{2-} sits at the top of the portal of CB-[6] host molecule. Further decrease in the $\text{K}^+-\text{CrO}_4^{2-}$ leads to complete desolvation of CrO_4^{2-} and a corresponding increased solvation of CB-[6] portals. Further, shortening of K^+-Cr bond lengths (from 6 Å onwards) leads to strongly favorable binding energies (Fig. 3).

From Fig. 3, we can estimate the barrier for the formation of CB-[6]- CrO_4^{2-} complex. Considering the CrO_4^{2-} to sit at 10 Å from K^+ ion, the calculated activation barrier for binding is ~ 17 kcal mol⁻¹. The origin of such barrier is expected due to (i) the solvent reorganization of the guest molecule, (ii) the portal opening of the host molecule and (iii) strong electrostatic repulsion between the negatively charged host and the portals of CB-[6]. The calculated relaxation energy of CB-[6] of the higher energy structure is 30 kcal mol⁻¹. Hence, geometric relaxation of the host molecule is crucial for effective binding of the incoming guest molecule. In Fig. 4, we have plotted the Mulliken charge at the chromium centre during the chromate binding process to CB-[6]. Except for the high energy structure, we note that the positive charge on chromium decreases gradually. This rapid decreasing charge at the chromium centre of CrO_4^{2-} may be due to the electrostatic repulsion between the portals of CB-[6] with the chromate anion. The portal oxygen pumps the electron from CB-[6] to chromium centre, leading to the decreased charge at the chromium centre.

In the complete optimized structure, the $\text{K}-\text{Cr}$ bond length is 2.98 Å, where the K^+ ion is slightly inside the CB-[6] due to favorable electrostatic interactions. In this structure, the portals of CB-[6] are decorated by a cyclic hydrogen bonded network formed by water molecules.

Finally, introduction of the second K^+ ion leads to the sealing of the portals with the encapsulated CrO_4^{2-} which could be effectively removed from the environment (Fig. 5). Due to the introduction of the second K^+ ion, the

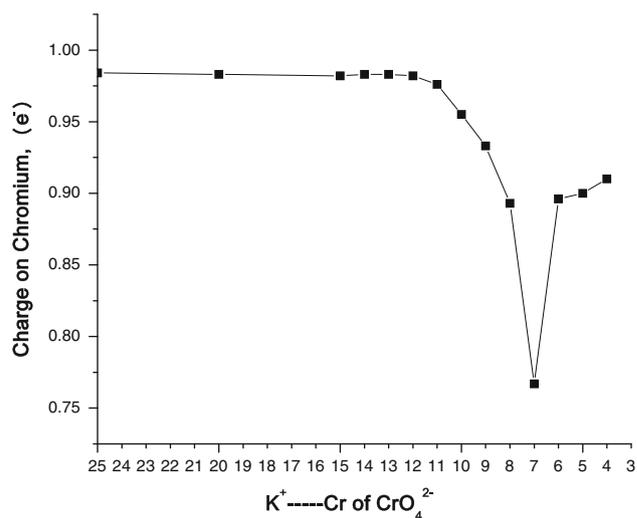


Fig. 4 Mulliken Charge (e^-) at chromium centre

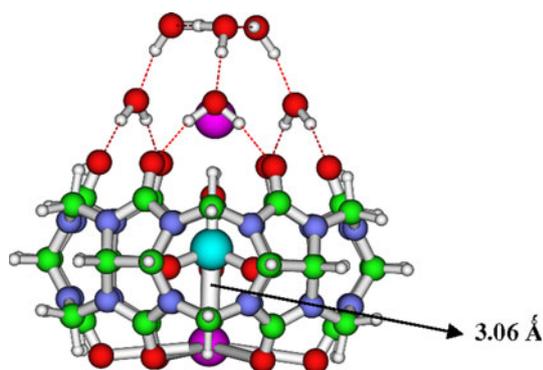


Fig. 5 Chromate sealed inside CB-[6] by two potassium ion

interaction between the CrO_4^{2-} and the first K^+ ion is slightly weakened (3.06 Å).

Conclusions

We have addressed the possibilities for favorable binding of negative charged species to CB-[6]. Since, the suggestion of Behrend et al. [4], no experimental or theoretical investigations were carried out on CrO_4^{2-} binding to CBs. This paper highlights the significance of portal opening of the host molecule and the important role played by metal ion for favorable binding. We have estimated a barrier around $\sim 17 \text{ kcal mol}^{-1}$ for the formation of CB-[6]- CrO_4^{2-} complex which arises from solvent reorganization, portal opening of CB-[6] and by electrostatic repulsion between the host and guest molecule near the portals.

Acknowledgments We thank Dr. T. Mukherjee for his kind support, KSKRA fellowship for funding and the BARC computer center for providing the high performance parallel computing facility (Ameya and Ajeya Systems). SKG gratefully acknowledges support from the INDO-EU project MONAMI.

References

- Levina, A., Lay, P.A.: *Coord. Chem. Rev.* **249**, 281 (2005)
- Assfalg, M., Bertini, I., Bruschi, M., Michel, C., Turano, P.: *Proc. Natl. Acad. Sci. USA.* **99**, 9750 (2002)
- Lovley, D.R., Phillips, E.J.P.: *Appl. Environ. Microbiol.* **60**, 726 (1994)
- Behrend, R., Meyer, E., Rusche, F.: *Justus Liebigs Ann. Chem.* **339**, 1 (1905)
- Freeman, W., Mock, W.L., Shih, N.-Y.: *J. Am. Chem. Soc.* **103**, 7367 (1981)
- El Haouaj, M., Ko, Y.H., Luhmer, M., Kim, K., Bartik, K.: *J. Chem. Soc. Perkin Trans. 2*, 2104 (2001)
- El Haouaj, M., Luhmer, M., Ko, Y.H., Kim, K., Bartik, K.: *J. Chem. Soc. Perkin Trans. 2*, 804 (2001)
- Buschmann, H.-J., Jansen, K., Meschke, C., Schollmeyer, E.: *J. Sol. Chem.* **27**, 135 (1008)
- Buschmann, H.-J., Cleve, E., Jansen, K., Wego, J.A., Schollmeyer, E.: *J. Incl. Phenom. Macrocycl. Chem.* **40**, 117 (2001)
- Liu, J.-Z., Long, L.-S., Haung, R.-B., Zheng, L.-S.: *Inorg. Chem.* **46**, 10168 (2007)
- Zhang, Y.-Q., Zhu, Q.-J., Xue, S.-F., Tao, T.: *Molecules* **12**, 1325 (2007)
- Pichierri, F.: *Chem. Phys. Lett.* **390**, 214 (2004)
- Pichierri, F.: *Chem. Phys. Lett.* **403**, 252 (2005)
- Pinjari, R.V., Gejji, S.P.: *J. Phys. Chem. A.* **112**, 12679 (2008)
- Gobre, V.V., Pinjari, R.V., Gejji, S.P.: *J. Phys. Chem. A.* **114**, 4464 (2010)
- Suvitha, A., Venkataramanan, N.S., Mizuseki, H., Kawazoe, Y., Ohuchi, N.: *N. J. Incl. Phenom. Macrocycl. Chem.* **66**, 213 (2010)
- Sundararajan, M., Campbell, A.J., Hillier, I.H.: *Faraday Discuss.* **48**, 195 (2011)
- TURBOMOLE V6.0, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH (1989–2007) TURBOMOLE GmbH, since (2007); available from <http://www.turbomole.com> (2009)
- Bryantsev, V.S., Diallo, M.S., van Duin, A.C.T., Goddard III, W.A.: *J. Chem. Theory Comput.* **5**, 1016 (2009)
- Carlqvist, P., Masaras, F.: *Chem. Commun.* 748 (2007)
- Zhou, J., Santambrogio, G., Brummer, M., Moore, D.T., Woste, L., Meijer, G., Neumark, D.M., Asmis, K.R.: *J. Chem. Phys.* **125**, 111102 (2006)
- Marquez, C., Hudgins, R.R., Nau, W.M.: *J. Am. Chem. Soc.* **126**, 5806 (2004)