

Host-guest interaction of cucurbit[7]uril with *para*-nitrophenol: A weakly binding inclusion complex

Sabyasachi Patra^{a,*}, Sudip Gorai^b, D Rama Mohana Rao^c,
Manoj K Sharma^d, Sandip K Nayak^b, Alok K Ray^e
& A Goswami^a

^aRadiochemistry Division, ^bBio Organic Division,
^cRadioanalytical Chemistry Division, ^dFuel Chemistry Division,
^eLaser & Plasma Technology Division, Bhabha Atomic
Research Centre, Trombay, Mumbai 400 085, India

Email: spatra@barc.gov.in; sspatra86@gmail.com (SP)

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Host-guest interaction between water soluble rigid molecular container cucurbit[7]uril (CB[7]) and a water soluble organic guest *para*-nitrophenol (PNP) has been investigated using ¹H NMR spectroscopy and isothermal titration calorimetry. The stoichiometry, binding constant and other thermodynamic parameters of complexation have been obtained which show the formation of weakly binding 1:1 inclusion complex resulting from enthalpy-entropy compensation. Cyclic voltammetry study of PNP-CB[7] complex in acidic pH reveals a large cathodic shift in the reduction potentials of PNP, indicating either stabilization of PNP or destabilization of the electro-reduced product inside CB[7] cavity.

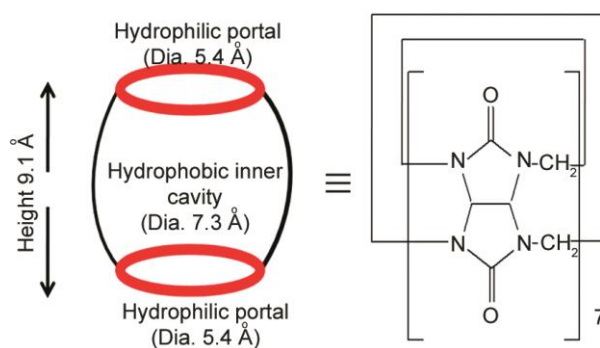
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Cucurbit[*n*]urils (CB[*n*] with *n* = 5-8, 10) are a class of structurally simple synthetic macrocyclic host with exceptional binding properties for varieties of guest molecules^{1,2}. Glycouril is the building block for CB[*n*], where *n* refers to the number of glycouril units in the molecule (structure **I**). Their shape is similar to that of pumpkins³ with carbonyl fringed portals and a hydrophobic cavity. The carbonyl oxygens have high electron density and can bind cations through the formation of coordinate bonds⁴. Lack of any polar functional group gives hydrophobic character to the inner cavity, whose size increases with *n* (5-8, 10). Because of the presence of hydrophobic cavity, they can act as artificial receptor, forming stable complexes with guests such as small organic molecules, drug molecules, amino acids, peptides, dyes, and hydrocarbons.

CBs have received considerable attention due to their promising applications in several fields such as molecular sensor, drug delivery, nanosized reaction vessels for carrying out selective chemical/photochemical reactions, and supramolecular catalyst⁵⁻⁷.

Use of CBs as water soluble molecular container for host guest complexations, controlled chemical reactions and catalysis has not been explored to the same extent as cyclodextrin. CB[7] is particularly suitable for these studies because of its significant water solubility and optimum cavity size for a wide range of guest molecules^{5,6,8-20}. Understanding the factors governing the strength of binding of CB[7] with various types of guest molecules, the effect of confinement of guest molecules on selectivity in chemical reactions, and modification of the chemical/electrochemical behaviours of guest molecules due to host guest binding are the area of current research interest. The experimental methods commonly used for the study of host-guest interaction are different types of microcalorimetry, various spectroscopic techniques such as UV-vis absorption, steady and time resolved fluorescence, NMR, FT-IR, ESR, and chromatographic techniques etc²¹.

In this work, the nature of host guest interaction between supramolecular host cucurbit[7]uril and organic guest, *p*-nitrophenol (PNP) in aqueous medium has been studied. The nature and stoichiometry of the host guest complex has been inferred from the results of ¹H NMR as well as isothermal titration calorimetry (ITC) experiments. The thermodynamic parameters of



Structure of cucurbit[7]uril

(I)

binding have also been obtained from ITC experiments and interpreted in terms of enthalpy-entropy compensation. Finally, the effect of host-guest binding on the redox behaviour of the guest molecule has been qualitatively investigated using cyclic voltammetry.

Experimental

The host cucurbit[7]uril and the guest, *p*-nitrophenol were purchased from Sigma Aldrich. All the chemicals were used without further purification. De-ionised water with specific resistance of 18 M Ω /cm, purified by model QuantumTM from Millipore, Mumbai, India was used throughout the work for preparing solutions.

¹H NMR titration of PNP with CB[7] in D₂O solution was carried out in a Bruker 200 MHz spectrometer with chemical shifts reported as ppm. For this purpose, 0.5 mL of PNP having concentration 1.28 mM was taken in a NMR tube. To that solution different molar proportion of CB[7] was added from a 10 mM stock solution of CB[7]. Molar ratios of PNP:CB[7] was varied as 1:0, 1:0.4, 1:0.8, 1:1 and 1:2.

The calorimetric experiment was carried out with an isothermal titration calorimeter (Nanocalorimeter Thermometric Assistance and Management, TAM-III, Thermometric AB, Sweden). It is a twin thermopile heat conduction type calorimeter, where the measured differential power signal was dynamically corrected for the thermal inertia of the system. The calorimeter consisted of a reaction and reference vessel, each of volume 4 mL. In order to minimize the short-term noise, the heat capacity of both the vessels was balanced by keeping same volume of solution in each container. The titrant was supplied to the reaction vessel through a stainless steel injection needle (length: 1 m and internal dia.: 1.5 \times 10⁻⁴ m) connected with a Hamilton syringe containing the titrant. The syringe was driven by Lund syringe pump. The temperature of the bath was maintained at 298 \pm 0.0001 K. The instrument was calibrated electrically and the performance of the instrument was tested by measuring log *K* and ΔH for the reaction between BaCl₂ and 18-crown-6 in water. For calorimetric titration of CB[7] with PNP, 2.7 mL aqueous solution of CB[7] having concentration of 0.008 M was taken in the reaction vessel and titrated with the guest PNP (0.1 M). The titrant (guest solution) was progressively added to the titre (host

solution) in the reaction vessel at multiple injections of 15 μ L each. The heat of dilution of titrant was determined in a separate calorimetric titration of the blank (only water) with the titrant solution. The net reaction heat Q_r^i at each step of titration was calculated using the equation, $Q_r^i = Q_{tot}^i - Q_{dil}^i$, where *Q* denotes the heat released and subscripts tot and dil represent the total and dilution heats of reaction at each injection. The calorimetric titration data, corrected for dilution, were analyzed to obtain the composition of the complex, binding constant and the thermodynamic parameters of complexation.

The electrochemical measurements were performed using a CHI 760D electrochemical workstation in a three-electrode cell. All the electrodes were obtained from CH Instruments, Inc. Gold electrode ($\Phi = 2$ mm) was used as the working electrode, while platinum wire and Ag/AgCl/3M KCl electrodes were used as the counter and the reference electrodes, respectively. The gold electrode was polished using alumina powder (CH Instruments, Inc.) paste of decreasing particle size from 1.0 to 0.05 μ m. The gold electrode was ultrasonically cleaned in water after each polishing step to remove any adhering alumina particles. High purity argon gas was purged through the solution for 10 min before each measurement. All potentials reported in this manuscript are with respect to Ag/AgCl/3M KCl.

Results and discussion

Figure 1 shows a portion of the ¹H NMR spectra of PNP in presence of varying ratios of CB[7]. The ¹H NMR of free PNP in D₂O shows a pair of doublets (AA'XX') due to the protons of the benzene ring. However, gradual addition of CB[7] to PNP leads to broadening of both the doublets with small up-field shift. The peaks are ultimately buried under the base line when the molar ratio of CB[7]:PNP exceeds 1. This clearly suggests inclusion of PNP within CB[7] cavity forming 1:1 complex. However, the binding constant of the complex could not be determined due to broadening of the characteristics ¹H NMR absorption peaks.

Figure 2 gives the titration calorimetric plot which shows variation of heat flow as a function of successive addition of PNP. It is seen that the heat flow saturates beyond [PNP]/[CB7] = 1 (nearly 6 hours onwards), indicating the formation

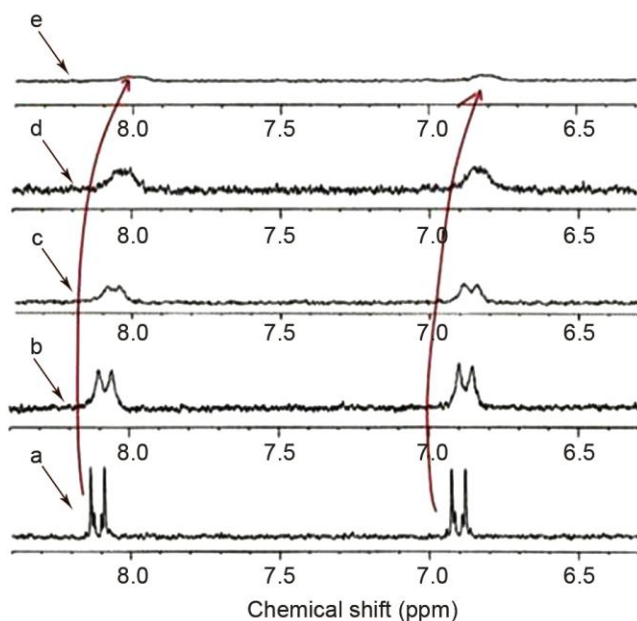


Fig. 1 – ^1H NMR signals of PNP (zoomed in chemical shift region of 6.3–8.5 ppm) in D_2O with different PNP:CB[7] ratios [(a) 1:0; (b) 1:0.4; (c) 1:0.8; (d) 1:1; (e) 1:2].

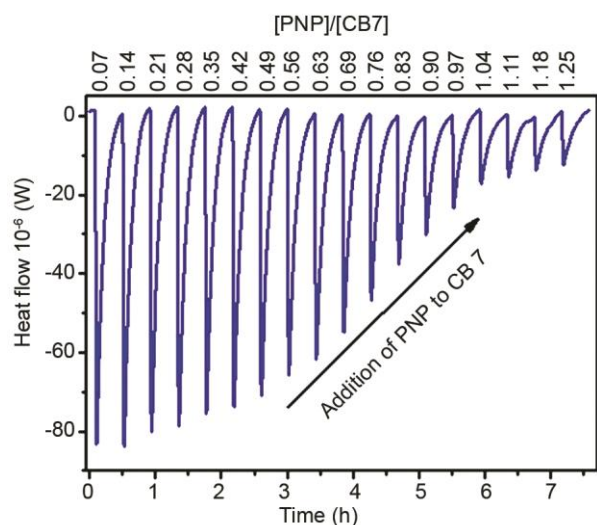


Fig. 2 – ITC data for the interaction of CB[7] with aqueous solution of PNP. $[\text{CB}[7]] = 0.008 \text{ M}$, $[\text{PNP}] = 0.1 \text{ M}$, $T = 298 \text{ K}$, cup vol. = 2.7 mL. Each peak corresponds to addition of 15 μL of 0.1 M PNP. The change in ratio of concentration $[\text{PNP}]/[\text{CB}[7]]$ during each addition is shown at top axis].

of 1:1 complex. This is also evident from the plot of net reaction heat (Q , mJ) versus $[\text{PNP}]/[\text{CB}[7]]$ ratio (Fig. 3). Binding constant (K), Gibbs free energy (ΔG), enthalpy of formation (ΔH) and entropy of formation (ΔS) of the inclusion complex are found to be $1.33 \pm 0.02 \times 10^3 \text{ M}^{-1}$, $-17.8 \text{ kJ mol}^{-1}$, $22.7 \pm 0.8 \text{ kJ mol}^{-1}$ and $135.987 \text{ J K}^{-1} \text{ mol}^{-1}$,

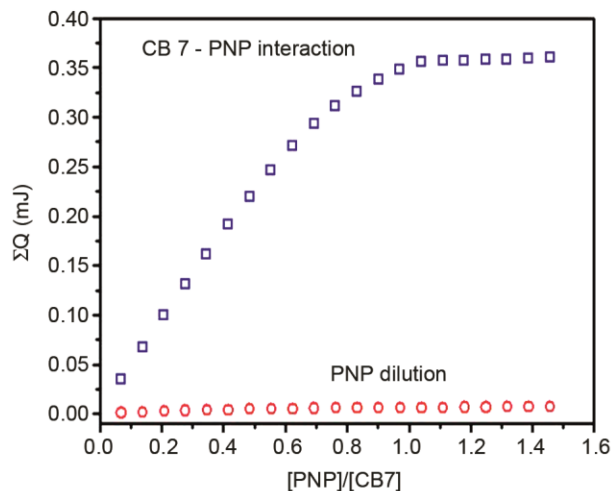


Fig. 3 – Variation of heat released as a function of PNP-to-CB7 mole ratio (squares) and the heat of dilution of PNP with water only (circles).

respectively. The value of binding constant suggests relatively weak binding of the CB[7]:PNP complex. This is also reflected in the relatively small up-field shifts (compared to literature data for many other inclusion complexes^{23–25}) and extensive broadening of the resonances of PNP's aromatic protons (Fig. 1) in the presence of CB[7]. From the value of binding constant and the concentration of PNP and CB[7] (0.008 M) it has been calculated that about 26% PNP remains free in solution at equilibrium in an equimolar mixture of PNP and CB[7]. The ^1H NMR and ITC results suggest that the structure of the PNP-CB[7] complex is not very well defined, that is, the guest is probably exchanging quickly over various partially or fully included locations in the host cavity, resulting in a complex with low thermodynamic stability. Binding constants for the host-guest complexes of CB[7] with a series of neutral small organic molecules are reported by Biedermann *et al.*¹⁰. The value of K , determined for the present system agrees with the reported values for small neutral guest molecules. It is to be noted that, UV-vis absorption spectrometry could not be used for the determination of binding constant in the present study because of negligible change in electronic absorption spectrum of the guest molecule (PNP) with increasing concentration of host (CB[7]).

Houk *et al.*²⁶ have analyzed the binding constant of a series of host-guest systems comprising cyclodextrins, synthetic hosts in water (example CB[7]), catalytic

antibodies and enzyme hosts and a variety of guests like neutral organic molecules, substrate, transition state, and drugs molecules. It has been inferred that the vast majority of the complexes involving such host and neutral organic molecules have dissociation constant ($1/K$) in the decimolar ($10^{-1} M$) to micromolar ($10^{-6} M$) range with mean value at $10^{-3} M$, indicating that these complexes show strong enthalpy entropy compensation behaviour, such that the free energy of complexation²⁶ remains around -15 kJ mol^{-1} , which agrees closely with the value obtained in the present work. The positive value of both ΔH and ΔS as obtained in the present case shows that the driving force for complexation is mostly entropic in nature and may be associated with the desolvation of the host and guest molecules.

Gadde and Kaifer²⁷ have recently reviewed the electrochemical behaviour of cucurbituril complex of viologen and ferrocene derivatives²⁷, which forms very strong complexes with CB[7] ($K > 10^6 M^{-1}$). However, electrochemical studies are limited for systems with lower binding constants. Since PNP is an electrochemically active guest molecule, possible modification of its electrode behaviour due to formation of inclusion complex with CB[7] has been studied.

Addition of CB[7] solution into 2 mM aqueous solution of PNP in equimolar proportion results in a decrease in pH of the PNP solution from 5.2 to 3.6 due to the presence of acid of crystallization in CB[7]. Cyclic voltammogram of 1 mM PNP at pH 3.6 at a scan rate of 0.05 V/s shows a well defined reduction peak (P1), followed by a wave at -0.36 V during the first cathodic sweep from 0.8 V to -1.2 V (Supplementary data, Fig. S1). An oxidation peak P2 appears at 0.55 V during the reverse scan. During the second cathodic sweep, another reduction peak P3 appears at 0.37 V , which forms a redox couple with P2. The mechanism of reduction of PNP on Au electrode²² is given in Scheme S1 (Supplementary data). Figure 4 gives the CV responses (2nd CV cycle) of 1 mM PNP recorded on a gold electrode ($\Phi = 2 \text{ mm}$) in absence and in presence of 1 mM CB[7] at pH 3.6 and at a scan rate of 0.05 V/s. It is seen that the cathodic peak (P1) for the reduction of HO-Ph-NO₂ to HO-Ph-NHOH is shifted by 0.17 V , and the formal potential ($E^{0'}$) for the free HO-Ph-N=O/HO-Ph-NHOH redox couple (P2/P3) is shifted by 0.28 V to more cathodic potential

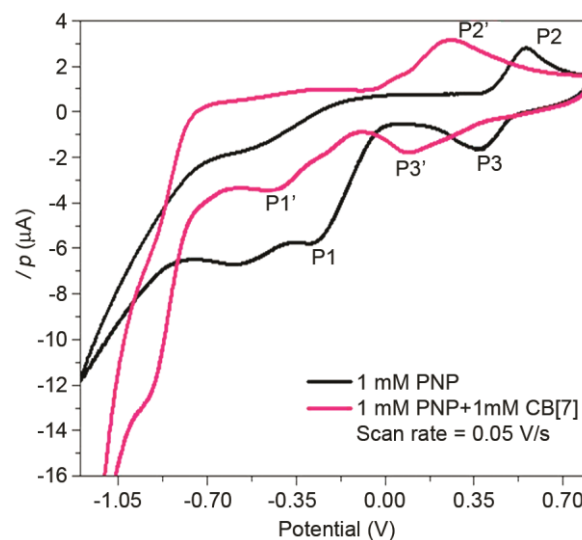


Fig. 4 – Cyclic voltammetry responses of 1 mM PNP recorded on a gold electrode ($\Phi = 2 \text{ mm}$) in the absence and in the presence of 1 mM CB[7] at pH 3.6 and at scan rate of 0.05 V/s. The curves represent the 2nd CV cycle.

upon interaction with CB[7]. This cathodic shift suggests that either PNP is stabilized by CB[7] or its reduced form is destabilized or a combination of both^{28,29}. As stated earlier, the low binding constant between CB[7] and PNP suggests the presence of free PNP and CB[7] in solution at equilibrium. Thus, the shifted CV peaks may result from the presence of a fast exchanging mixture of free, partially included and fully included complexes.

In the present study, the low value of binding constant as obtained from ITC study ($10^3 M^{-1}$) and results of ¹H NMR suggest the formation of a complex with low thermodynamic stability. The positive values of both ΔH and ΔS for complexation, as obtained from ITC experiment, show the dominance of entropy change during complexation, which points to the effect of strong enthalpy entropy compensation. Binding constant (K) of the complex indicates that a significant fraction of host and guest remain free at equilibrium. The molecular encapsulation of PNP in the CB[7] cavity results in a significant cathodic shift of its CV peaks, which shows either PNP is stabilized or its reduction product is destabilized in CB[7] cavity.

Supplementary data

Supplementary data associated with this article, Fig. S1 and Scheme S1, are available in the electronic form at [http://www.niscair.res.in/jinfo/ijca/IJCA_56A\(05\)508-512_SupplData.pdf](http://www.niscair.res.in/jinfo/ijca/IJCA_56A(05)508-512_SupplData.pdf).

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