An Analysis of an Induced-Fit Type Inclusion Phenomenon of a Paracyclophane with Benzene by Means of van der Waals Potential Calculations

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Abstract. The binding process of the paracyclophane 1 with benzene is classified into two types; namely simple fit and induced fit. In the former case, it is assumed that the geometry of the host is fixed to that in the free state during complexation. On the basis of the MMP2 calculations, the induced fit type process, allowing all motional freedoms of the host and the guest, is essential in forming the stable 'inclusion' complex with benzene. By the use of van der Waals potential maps, it is confirmed that the force-field inside the cavity of the host is effective for the inclusion of benzene.

1. Introduction

Cyclophanes (CP's) are macrocyclic compounds containing benzene rings linked in their macrocyclic skeletons. Paracyclophanes (PCP's) have a deep cavity surrounded by benzene rings in a 'face to face' conformation [1]. Their cavities are hydrophobic. For example, the polarity of the cavity of N,N',N'',N'''-tetramethyl-2,11,20,29-tetraaza[3.3.3.3]PCP (N_4PCP: Figure 1) is approximately the same as that of a 50% $C_2H_5OH-H_2O$ mixture [2]. PCP's can selectively form inclusion complexes with guest molecules [2–5]; for example, a PCP consisting of two diphenylmethane units forms stronger complexes with aromatic guests than with aliphatic ones [6, 7].

Interactions between many macrocyclic compounds and guest molecules have been studied by the MMP2 method and have successfully explained the host–guest specific interaction [10–12]. In a previous paper [8], on the basis of MMP2 calculations, we have shown the N_4PCP interacts more strongly with an aromatic guest (benzene) than with aliphatic ones (dichloromethane, ethanenitrile, and propane) through an induced-fit type of binding mechanism. We have suggested that induced-fit type conformational change is driven by the host–guest intermolecular van der Waals interaction. In this paper, the energetics of the inclusion phenomenon are studied in more detail and the origin of guest selectivity is accounted for using van der Waals maps for the cavity of N_4PCP.
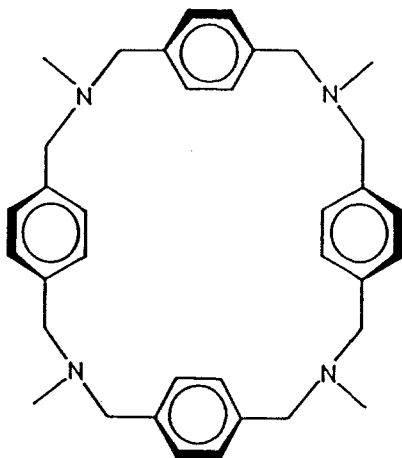
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Fig. 1.   Chemical structure of N,N',N'',N'''-tetramethyl-2,11,20,29-tetraaza[3.3.3.3]PCP.

2. Calculation

In this study, the MMP2 molecular mechanics methods [9] were used to obtain energy-minimum structures of N_4PCP and its complexes with benzene. The geometry in the free state was determined by the use of the X-ray structure of N_4PCP complexed with CH_2Cl_2 [13]. The inclusion process was classified into the following two types. One is 'simple fitting' where, during optimization, the geometry of the N_4PCP molecule is fixed to its optimized geometry in the free state (N_4PCP(i)). In other words, only benzene (guest) in the N_4PCP(i) cavity has a motional freedom during optimization. The initial geometry is assumed as follows: one [C(1)] of the carbon atoms of the guest benzene is located at the center of gravity of N_4PCP(i) and the C(1)—C(4) axis of guest benzene is on the line of the fourfold (C_4) symmetry axis of N_4PCP(i). The C(4) atom is a *para* carbon atom against the C(1) atom in the benzene molecule. The other process is relevant to the so-called 'induced fitting'. In this case, the final geometry resulting from the simple-fit process was further optimized with all the freedoms of N_4PCP and benzene being allowed.

In order to visualize properties of the cavities of N_4PCP(i) and N_4PCP(c), van der Waals potential maps were obtained. Here, N_4PCP(c) means the N_4PCP molecule having a geometry optimized through the induced-fit process. The van der Waals potential at a certain point was defined as the sum of the van der Waals energies between a probe (hydrogen) atom located at this point and all atoms of the N_4PCP molecule. The van der Waals potential energy was calculated using Allinger's force field adopted in the MMP2 method [9]. The maps were drawn on the average molecular plane, defined as the plane perpendicular to the molecular symmetry axis and containing the center of gravity. The maps for the guest benzene were drawn on a plane which involves the C(1)—C(4) axis and is perpendicular to the molecular plane.

3. Results and Discussion

There are at least three distinct states to be considered for the complexation of
N_4PCP with benzene. The first is the initial state, where the guest benzene is isolated
from the host N_4PCP. The second and the third are the states resulting from the
simple and induced fittings, respectively. The energy diagram of the inclusion
process is shown in Figure 2. The steric energy (E_s) of the 'imperfect' N_4PCP–
benzene complex, i.e. the simple-fit complex, is -12.40 kJ mol^{-1}. This complex is
more stable than the initial state by 34.44 kJ mol^{-1}. The steric energy (E_i) of the
'perfect' N_4PCP–benzene complex, i.e. the induced-fit complex, is -13.90 kJ mol^{-1}.
The net energy gain ($E_s - E_i$) from the induced-fitting is slight (1.5 kJ mol^{-1}). This
insignificant contribution is due to the increase in the steric energy of the host itself
through the induced fit process. The increment (E_{conf}) can be evaluated as the
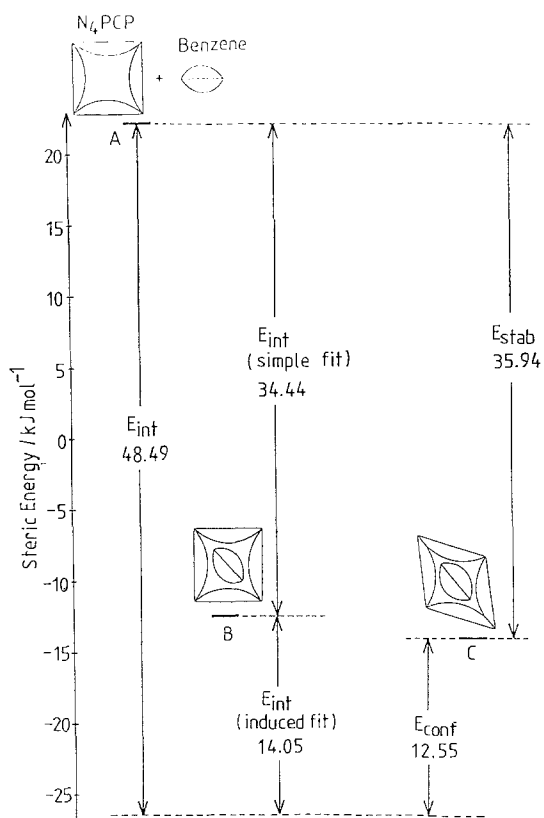difference in the steric energies between N_4PCP(c) and N_4PCP(i), which are 45.78

Fig. 2. The energy diagram of the inclusion process of N_4PCP with benzene; A: the isolated state of
N_4PCP and benzene; B: imperfect (simple fit) complex state of N_4PCP and benzene; C: perfect (induced
fit) complex state of N_4PCP and benzene. E_{int} (simple fit) and E_{int} (induced fit) are the interaction energy
between N_4PCP and benzene for simple fit and induced fit, respectively. E_{int} is the sum of E_{int} (simple
fit) and E_{int} (induced fit). E_{stab} is the stabilization energy of the complex relative to the isolated state. E_{conf}
is an increase in steric energy of the host by conformational change upon induced-fitting.

and 33.23 kJ mol^{-1}, respectively. N$_4$PCP(c) is thus less stable than N$_4$PCP(i) by 12.55 kJ mol^{-1}. Using these data, we can calculate the host–guest interaction energy (E_{int} (induced fit)) in the induced fit complex as follows:

$$E_s + E_{int} \text{ (induced fit)} + E_{conf} = E_i.$$

Consequently, we obtain -14.05 kJ mol^{-1} as the value of E_{int} (induced fit), the contribution of which is 30% of the total interaction energy ($E_{int} = -48.49$ kJ mol^{-1}).

The final geometries of the simple-fit and induced-fit complexes are shown in Figures 3 and 4, respectively. The N$_4$PCP—benzene complex in the induced-fit state is a true 'inclusion' complex, where the benzene molecule is deeply included into the N$_4$PCP cavity. The C(1)—C(4) axis of benzene agrees with the center axis (C$_2$ axis) of N$_4$PCP. On the other hand, in the simple-fit state, the benzene molecule protrudes from the N$_4$PCP cavity. The C(1)—C(4) axis of benzene does not agree
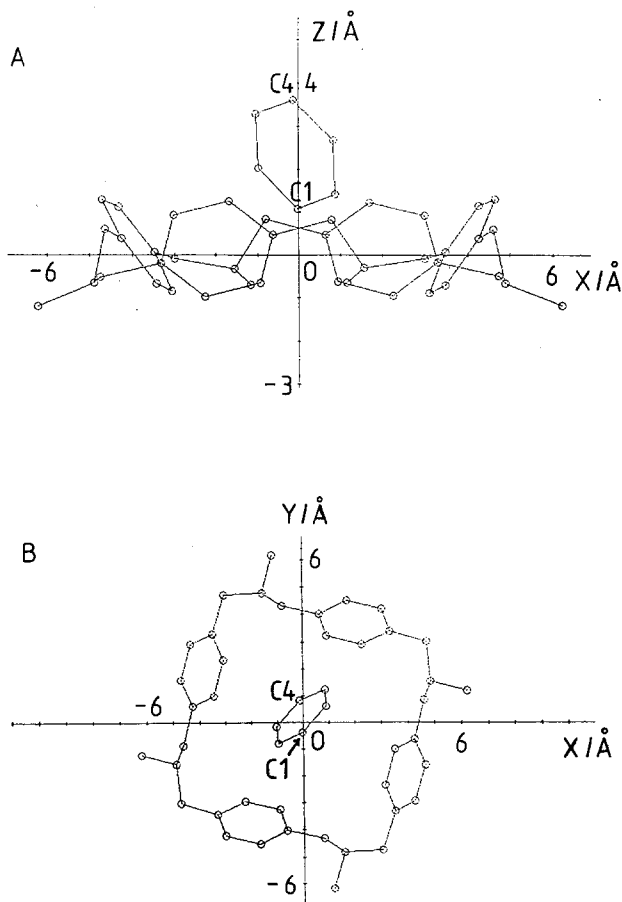

Fig. 3.   The schematic illustration of the N$_4$PCP–benzene complex after simple fit, showing the views of the XZ (A) and XY planes (B). The z-axis is on the C_4 axis of N$_4$PCP(i).
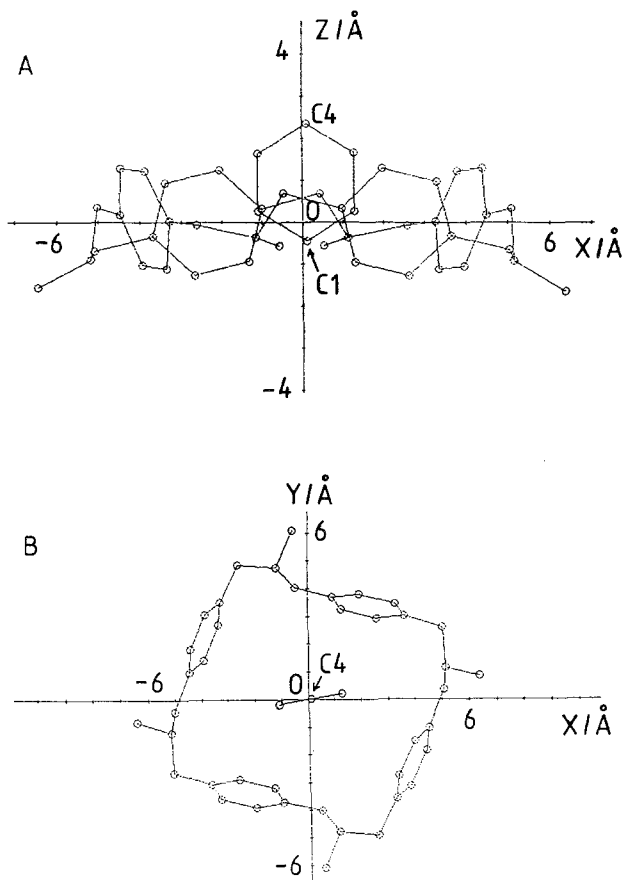
Fig. 4. The schematic illustration of the N_4PCP–benzene complex after induced fit, showing the views of the XZ (A) and XY planes (B). The z-axis is on the C_2 axis of N_4PCP(c).

with the center axis of the N_4PCP cavity. Therefore, the induced fitting is indispensable for N_4PCP in forming the 'inclusion' complex with benzene. The induced fitting plays a key role in attracting a benzene molecule (guest) from solution containing benzene.

According to our previous report [8], van der Waals interaction is the main binding force for complexation of N_4PCP with benzene. In order to ascertain the complementarity in the van der Waals potentials between the host and the guest molecules, their potential maps were illustrated. The results for N_4PCP(i) and N_4PCP(c) are shown in Figures 5 and 6, respectively. The shapes of the energy contours are square inside the cavity of N_4PCP(i), which reflects the fact that the skeletal conformation of N_4PCP(i) is a nearly regular square. The optimized conformation of N_4PCP(c) is a rhombus [8]. As a result of this, the shapes of the contours change from square to rectangle, and the symmetry around the center axis changes from C_4 to C_2 upon induced fitting. The van der Waals potential map for benzene is shown in Figure 7. The potential wells are located near the center of the
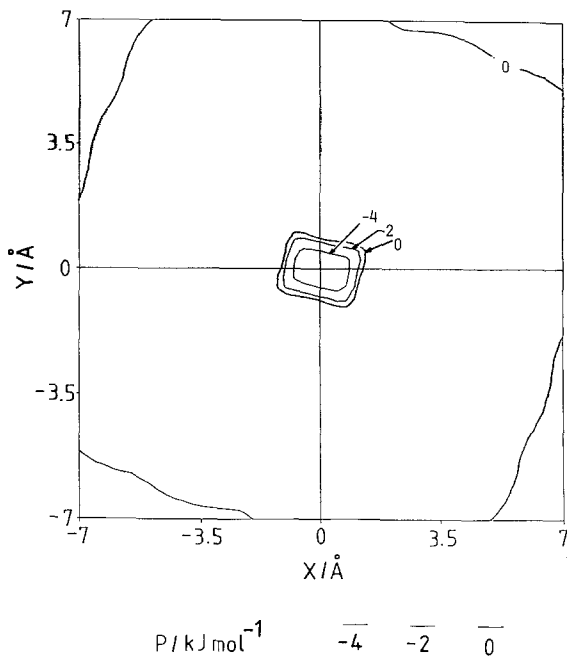
Fig. 5. Van der Waals potential on the XY macrocyclic plane involving the center of the gravity of N$_4$PCP in the isolated state. The definition of coordinates is shown in Figure 3.
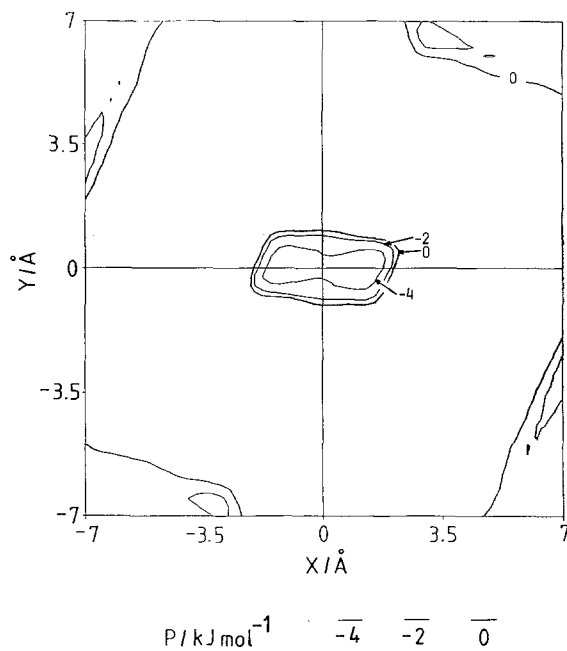

Fig. 6. Van der Waals potential on the XY macrocyclic plane involving the center of the gravity of N$_4$PCP cavity in the state of complex with benzene. The definition of coordinates is shown in Figure 4.
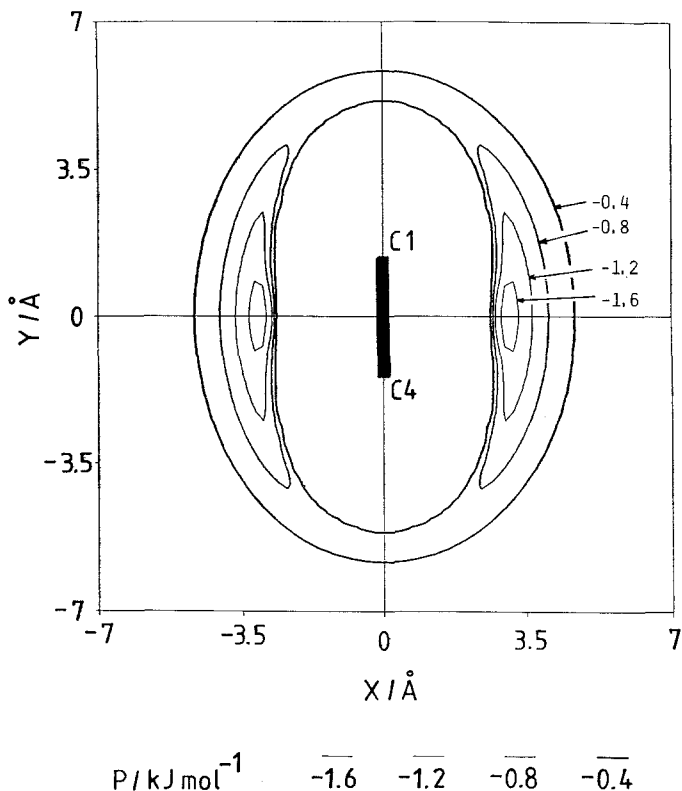
Fig. 7.   Van der Waals potential of a single benzene molecule on the plane which is perpendicular to the benzene plane and involves the $C(1)-C(4)$ axis.

molecule on both sides with respect to the molecular plane. The overall shape of the potential distribution is elliptical on the XY plane. It is thus apparent that the guest benzene is more favourably fitted to the cavity of $N_4PCP(c)$. In addition, the guest could not penetrate into the cavity of $N_4PCP(i)$ owing to the disagreement in symmetry between them.

In conclusion, the induced fit does not largely contribute to the energy gain for the stabilization of the complex. Its principal role is to change the shape of the force-field inside the cavity and hence to permit more tight fitting between the host and the guest molecules, which is clearly shown from the van der Waals potential maps.

Acknowledgements

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