A kinetic study of C_{60}/γ-cyclodextrin inclusion complexation by molecular mechanics

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The inclusion complexation kinetics of C_{60} + γ-CD → C_{60}/γ-CD, C_{60}/γ-CD + γ-CD → C_{60}/(γ-CD)$_2$ and C_{60} + γ-CDN$^+$ → C_{60}/γ-CDN$^+$ are investigated by molecular mechanics.

Cyclodextrins (CDs), cyclic oligomers of glucose, and their derivatives have been widely studied because of their use as hosts in molecular recognition.[1] Fullerenes have also received much attention from the scientific community due to their novel structures and useful properties,[2] especially their biochemical applications *e.g.* possible inhibition of HIV-1 protease by C_{60} derivatives.[3] In association with biomimetic studies, molecular recognition of C_{60} with γ-CD in aqueous solution has been recently reported by several groups.[4–7] C_{60} is highly hydrophobic and insoluble in water. However, since C_{60} can interact with the cylindrical hydrophobic cavity of γ-CD which shows high water solubility, the inclusion complex C_{60}/γ-CD is water soluble. The structure of the most stable complex C_{60} with γ-CD was reported to be C_{60}/(γ-CD)$_2$, in which C_{60} is bicapped by two γ-CDs.[4,5,7] Recently, the kinetic behaviour of the complexation of C_{60} with γ-CD and its derivative in aqueous solution was reported.[7] The rate constant of C_{60} + 2 γ-CD → C_{60}/(γ-CD)$_2$ complexation showed first-order dependency on the concentration of γ-CD. Therefore a two step reaction mechanism was suggested, and the rate-determining step of the complexation reaction must be the first step, the 1 : 1 complex formation step, C_{60} + γ-CD → C_{60}/γ-CD. On the other hand, 6-trimethylammonium-6-deoxy-γ-cyclodextrin chloride(γ-CDN$^+$), which is a more water soluble host molecule, did not undergo complex formation with C_{60}. Here we report our findings on the complexation reaction of C_{60} with γ-CD and γ-CDN$^+$ using molecular mechanics calculations, and elucidate the experimentally reported kinetic complexation behaviour.

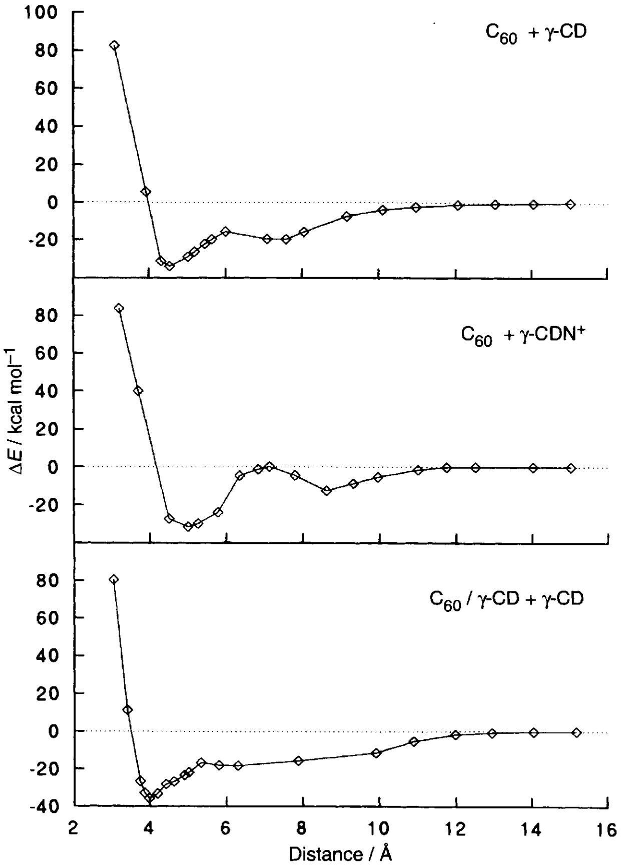

Fig. 1 Total energy change along the inclusion complex formation reaction path of C_{60} + γ-CD, C_{60}/γ-CD + γ-CD and C_{60} + γ-CDN$^+$. $\Delta E[C_{60}$ + γ-CD] = $E[C_{60}$/γ-CD] − ($E[C_{60}]$ + E[γ-CD]). $\Delta E[C_{60}$ + γ-CDN$^+$] = $E[C_{60}$/γ-CDN$^+$] − ($E[C_{60}]$ + E[γ-CDN$^+$]). $\Delta E[C_{60}$/γ-CD + γ-CD] = $E[C_{60}$/(γ-CD)$_2$] − ($E[C_{60}$/γ-CD] + E[γ-CD]).

For this work we used the Insight II/Discover molecular modelling package program.[8] The AMBER force fields[9] with extension of Homans' carbohydrate force fields,[10] which can account for the anomeric effect associated with carbohydrates, were used with the AMBER charge option for CDs. The C_{60} molecule was optimized with the AMBER force fields and charges obtained with a PM3 calculation.[11] The molecule energies were obtained by full optimization through conjugate gradient method. The calculations did not take into account water molecules. At first the structures of γ-CD and C_{60} were optimized separately. The energy changes during the C_{60}/γ-CD inclusion complexation were determined from the energies of the optimized geometry of the complex at fixed distances between the centre of the C_{60} molecule and the centre of the γ-CD molecule which is the centre of mass of the eight oxygen atoms on the glycosidic linkages. The minimum energy complexation path is on the cylindrical axis of γ-CD. In order to test the quality of the program and the force fields for the CDs, we calculated the structures of α-, β-CD with water molecules inside the cavity. The bond lengths and angles of the optimized structures were compared with those obtained from X-ray diffraction data.[12,13] The differences were in the standard deviation of the X-ray analysis. The optimized structure of C_{60} showed that the two C–C bondlengths were 1.40 and 1.41 Å (experimental values 1.40 and 1.45 Å), and the sphere radius was 6.9 Å (experimental value 7.0 Å).[2] In order to find the complexation reaction path, we carried out molecular dynamics calculations with many different initial geometries around the reaction path.

Table 1 The activation barrier height (E_a) and the distances between the C_{60} and the γ-CDs at two minimums and a barrier for the inclusion complexation

	C_{60} + γ-CD	C_{60}/γ-CD + γ-CD	C_{60} + γ-CDN$^+$
E_a/kcal mol^{-1}	3.87	1.60	15.30
$r_{lm}{}^a$/Å	7.59	6.29	8.62
$r_b{}^b$/Å	6.00	5.33	7.13
$r_{gm}{}^c$/Å	4.54	3.99	5.00

[a] Distance at the local minimum. [b] Distance at the activation barrier. [c] Distance at the global minimum.

Table 2 Changes in the total energy and their components on the formation of inclusion complexes at two minimums and a barrier

Energy change[a]/ kcal mol^{-1}	C_{60} + γ-CD → C_{60}/γ-CD			C_{60} + γ-CDN^+ → C_{60}/γ-CDN^+		
	Global min.	Barrier	Local min.	Global min.	Barrier	Local min.
ΔE_{vdw}	−44.20	−25.38	−20.20	−44.20	−8.77	−17.49
ΔE_{es}	2.79	2.72	0.00	1.67	1.40	−0.03
ΔE_{int}	7.33	7.40	1.29	6.95	4.98	−0.17
ΔE_{hb}	−0.32	−0.31	0.00	0.0	0.0	0.0
ΔE_{tot}	−34.40	−15.93	−19.81	−35.38	−2.39	−17.69

[a] ΔE_{tot} value consists of ΔE_{vdW} (van der Waals), ΔE_{es}(electrostatic), ΔE_{int}(internal) and ΔE_{hb}(hydrogen bonding). ΔE is the difference between the energy of the inclusion complex and the sum of the energies of its constituents.

In order to investigate the kinetics of the inclusion complexation, we calculated the energy changes along the reaction path. For the C_{60}/γ-CD and C_{60}/γ-CDN^+ inclusion complexations, the C_{60} molecule was pulled into the γ-CD along the centre axis which threads the γ-CD ring. For the C_{60}/(γ-$CD)_2$ complexation, a two step mechanism was assumed, the second step being that the C_{60}/γ-CD forms a complex with another γ-CD. The energy changes along the complexation path are shown in Fig. 1. Two minimums and a potential barrier along the reaction path were observed for all three reactions, at which points the distances between the C_{60} and γ-CDs are given in Table 1. As the C_{60} molecule approaches γ-CD, the energy decreases at first, then goes through a barrier, and finally forms the most stable inclusion complex. The barrier heights, which correspond to activation energies for the complexation reactions, are also given in Table 1. The values for C_{60} + γ-CD, C_{60}/γ-CD + γ-CD and C_{60} + γ-CDN^+ are 3.87, 1.60, and 15.30 kcal mol^{-1} respectively (1 cal = 4.184 J). In the complexation of C_{60} and two γ-CDs, the activation energy of the first step, C_{60} + γ-CD → C_{60}/γ-CD, is higher than that of the second step, C_{60}/γ-CD + γ-CD → C_{60}/(γ-$CD)_2$. Therefore the rate-determining step should be the first step for the C_{60} bicapped inclusion complexation with two γ-CD molecules which is in agreement with the experimental result.[7] There is a much higher activation energy for the C_{60} + γ-CDN^+ reaction, which is also consistent with the experimental results.[7] The most stable complex, C_{60}/(γ-$CD)_2$, is almost symmetrical. The distances between C_{60} and both γ-CDs are close to 4.0 Å, and both γ-CDs have C_1 symmetry.

The energy changes during the formation of C_{60}/γ-CD and C_{60}/γ-CDN^+ inclusion complexes are shown in the Table 2. The main energy source for inclusion complexation is the van der Waals interaction between C_{60} and γ-CDs. The reason for the complexation to have a barrier seems to be that the most stable conformation of γ-CDs is not a highly symmetric circular structure. Previous molecular mechanics studies also reported that γ-CDs are not rigid and that symmetry breaking lowers the energy.[14] Therefore, in order to make an inclusion complex with highly symmetric C_{60}, γ-CD should have a more symmetric conformation to fit C_{60} in its cavity. Internal strain energy is therefore required to make the conformation of γ-CD more symmetric. In Table 2, our calculations show that the internal energy contribution to the total energy change is much bigger at the barrier than at the local minimum. The total energy differences of the most stable conformation of the inclusion complexes C_{60}/γ-CD and C_{60}/γ-CDN^+ from their constituent molecules are −34.40 and −35.38 kcal mol^{-1}, respectively, which show similar thermodynamic stability. However, the activation barrier for complexation of C_{60} + γ-CDN^+ is much higher than that of C_{60} + γ-CD. If we compare the energy components between the C_{60} + γ-CD and the C_{60} + γ-CDN^+ reactions, each component of the C_{60} + γ-CDN^+ reaction is a little bit smaller than each of the corresponding components of the C_{60} + γ-CD reaction, except the van der Waals component. This is attributed to the longer distance between the C_{60} and γ-CDN^+ at the barrier of the C_{60} + γ-CDN^+ reaction, Table 1. The absolute value of the van der Waals energy contribution to the total energy for the C_{60} + γ-CDN^+ reaction at the barrier is much smaller than that for the C_{60} + γ-CD reaction. From our calculated geometry, secondary hydroxy groups of γ-CD, which are attached to the opening ring, are orientated to the outside of the γ-CD ring. However, the structure of γ-CDN^+ at the barrier shows that one of the secondary hydroxy groups, which is placed just above the NMe_3^+ group, directs to the inside central axis of the γ-CD ring. This hydroxy group can give rise to the larger repulsion energy, hence the smaller non-bonded energy contribution for the C_{60} + γ-CDN^+ reaction at the barrier. The electrostatic interaction between the C_{60} and γ-CDs also contributes to the total energy change. However, this contribution is much smaller compared to the van der Waals and internal energies. In our calculations we did not include water solvent molecules around the complex which might affect the calculated total energies. However, the total energies due to water solvent molecules are expected to be similar during complexation since there is no significant change to the charge distributions of the complex in polar solvent. Therefore, there will not be substantial errors in the total energy change along the reaction path due to the lack of solvent.

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