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A computational study of the inclusion processes of cyclodextrins and cyclodextrin polymers

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A COMPUTATIONAL STUDY OF THE INCLUSION PROCESSES OF CYCLODEXTRINS AND CYCLODEXTRIN POLYMERS

By

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ABSTRACT

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Cyclodextrins (CDs) are molecules that are composed of glucopyranose rings. Cyclodextrins can be formed from either 6, 7, or 8 glucopyranose units yielding, α-, β-, or γ-Cyclodextrins respectively. Cyclodextrin polymers (CDPs) can occur when glyceryl linkers are added to the previously mentioned cyclodextrins. CDs and CDPs are hydrophilic, yet contain a hydrophobic cavity. This cavity allows for the binding of numerous guest molecules. Some practical purposes resulting from the host-guest interactions can be seen in cosmetology, food science, and pharmacy.

Using the MacroModel Interactive Molecular Modeling System Version 5.0 we studied the binding of guest molecules to α-, β-, and γ-CDs and CDPs. P-nitrophenol and p-hydroxylmethyl benzoate are bound to α-CD and α-CDP, a single pyrene is bound to β-CD and β-CDP, while two pyrenes can bind to the large cavity of γ-CD and γ-CDP.

For all three CDPs, the number of glyceryl linker units was systematically varied from one to ten to look at the effect of chain length on the stability of clam-shell versus open-binding. Each structure is minimized

in both a clam shell conformation, with the guest surrounded by two CDs connected by glyceryl linker units and in an open conformation, with the guest bound to only one CD of the CDP. An "inverted" position for open binding was also studied in α-CD and α-CDP. This position occurs when the ester group of p-hydroxylmethyl benzoate and nitro group of p-nitrophenol bind to the CD or CDP as opposed to the hydroxyl groups.

The results obtained show that open binding is most stable for α-, β-, and γ-CDPs for all chain lengths, and that there is no optimal value or glyceryl units for clam-shell binding. The determination of whether the "inverted" position in open binding is preferable to the "normal" position is inconclusive.

ACKNOWLEDGMENTS

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James A. Best

TABLE OF CONTENTS

INTRODUCTION

The development of numerous software packages such as MacroModel Interactive Modeling System has helped the field of chemistry to take a giant leap forward. The use of computational chemistry to study such molecules as cyclodextrins, and cyclodextrin polymers will most likely prove to be invaluable.

Cyclodextrins, which are torroidal-shaped molecules, are cyclic oligosaccharides.[1,2] They consist of D(+)-glucopyranose rings joined by α-(1,4) glycosidic linkages.[3,4,5,6,7,8] Cyclodextrins can be formed from either six, seven, or eight glucopyranose units, yielding α- , β- , and γ- cyclodextrins (αCD, βCD, and γCD) respectively.[2,4-8] See Figures 1-3 for αCD, βCD, and γCD. All of these cyclodextrins can form polymers (αCDP, βCDP, and γCDP). Some examples of CDPs can be seen in Figures 8-11. This occurs when a glyceryl chain of the formula $(CH_2\text{-}CHOH\text{-}CH_2\text{-}O)_n$ is attached to the cyclodextrin.[4,7-9] The number of glyceryl units, n, varies from one to twenty-four in the polymers. See Figure 7 for an illustration of a glyceryl linker unit.

Cyclodextrins are hydrophilic on the outside of the torrus, since all of the hydroxyl groups are pointed outwards.[2,5] However, they are hydrophobic within their internal cavity.[3,5] This feature allows for the inclusion of a variety of smaller organic guest molecules.[1,10] The guest molecules bind to the interior of the CD without the formation of covalent bonds.[6] The forces that are

involved in these inclusion processes are hydrogen and hydrophobic bonding, as well as dipole-dipole interactions.[10]

Some specific molecules that bind to α-cyclodextrins are p-hydroxylmethyl benzoate, or p-hmb (Figure 4), and p-nitrophenol, or p-np (Figure 5).[8] β-cyclodextrins have a larger cavity, hence larger guests, such as pyrene (Figure 6), can bind.[1,7] γ-cyclodextrins, like their β counterparts, can also bind pyrene, but the cavity within the γ-cyclodextrins is large enough to fit two pyrene molecules.[7,11,12]

Binding to a cyclodextrin polymer is postulated to occur in two different ways. One configuration is called clam-shell binding. This occurs when two cyclodextrins trap, or encapsulate the guest molecule. For this method to occur there must be at least a 2:1 ratio of host (cyclodextrin) to guest molecules. Illustrations of beta and gamma CDPs in the clam-shell binding conformation can be seen in Figures 10 and 11 respectively. The second type of formation is termed open-binding. This transpires when only one cyclodextrin interacts with the guest, such as when the host and guest molecules are present in a ratio less than 2:1.[1,4,7-9] Examples of open binding can be found in Figures 8 and 9.

Cyclodextrins serve many functions, and have numerous practical purposes. Some of these include the ability to enhance the solubility of organic molecules in water, and the improvement of separations in High Performance Liquid Chromatography.[4,7] Cyclodextrins are also useful in promoting the volatility, handling, and application of insecticides.[6] They can be used in

cosmetology, food science, and pharmacy, including the ability to have an inhibiting effect on the replication of HIV-1 in vitro, as well.[6,10,13]

It is evident that cyclodextrins serve many note-worthy purposes. What is not so apparent, however, is which of the numerous conformations of cyclodextrins is the most stable, and most suitable for such purposes as the aforementioned applications. This study attempts to determine the optimal glyceryl chain length for each polymer, and the prevalence of both the clam-shell and open-binding conformations as a function of glyceryl chain length.

EXPERIMENTAL METHODS

The program that was used for analysis of αCD, βCD, and γCD as well as the alpha, beta, and gamma cyclodextrin polymers was the MacroModel Interactive Molecular Modeling System Version 5.0 installed on a Silicon Graphics Indigo^2 workstation.[14]

The first step in the experiment involved the construction of the molecules to be studied. This was done upon obtaining alpha, beta, and gamma cyclodextrins from the Cambridge structural database.[15] A glyceryl chain of ten units was created, as well as p-hydroxylmethyl benzoate, p-nitrophenol, and pyrene. For the construction of the polymers, the glyceryl chain was attached to two cyclodextrins for modeling purposes. In reality, a CDP can have numerous CDs as well as a glyceryl chain from one to twenty-four units, but for our study the number of CDs was kept constant, and the number of glyceryl units was systematically varied from one to ten. Upon completion of the construction of each of these molecules, energy minimizations were performed. This process involved calculating the energy of each molecule initially, and then changing its command file to allow batch minimization jobs to be run. Once minimized, the various structures were assembled and minimized again providing energy values that were used to determine the prevalent binding conformation, and the optimal glyceryl chain length.

To do calculations with MacroModel, the following steps were followed. To create the αCDP, βCDP, and γCDP files the cyclodextrins obtained from the database, as well as all other files created, were opened by clicking on the READ command with the left or primary mouse button. The command was located in the Main Button Panel. This brought up the Read Panel, and again the primary mouse button was used to click on the OPEN command. The results of this action were to open up the Read Selector Panel. This in turn allows one to choose a directory, when clicking on either /usr/people/bestj/acdgly, or the α directory, /usr/people/bestj/bcdgly, which was the β directory, or /usr/people/bestj/gcdgly; the γ directory. After highlighting the file of choice, the FILTER command was the next button that needed to be depressed. This allowed for the selection of the file, and when pressing the OPEN READ command the molecule appeared on the screen.

Once the CD's had been saved the construction of the guest molecules as well as the glyceryl chain was necessary. The DRAW function in the Main Button Panel, was used to create carbon structures. To change carbons to oxygens, click on O in the Main Button Panel, then click on a carbon in the view screen. To change single bonds to double bonds, draw a second bond between the appropriate atoms. The WRITE command in the Main Button Panel allowed files to be saved simply by entering a filename, and clicking WRITE. An OVERWRITE function was also possible. These commands and instructions were used to create all the guest molecules and a glyceryl chain of ten linkages.

To construct the cyclodextrin polymers, the file that contained ten glyceryl linkages was initially opened. The HOLD1 function was used to copy the glyceryl units into the cyclodextrin files. This was possible by pressing deposit after choosing the HOLD1 function. The next step was to open the respective cyclodextrin files and choose the HOLD1 function again. This was followed by choosing the retrieve command, and making the choice not to delete the current structure. The same process was used again to copy guest molecules into their respective host files, after the glyceryl chains had been edited.

The primary mouse button was used to select the DELETE command in the Main Button Panel when editing the glyceryl chains. The next step was to drag the mouse onto the specific C-C, C-O, C-H, and O-H bonds that needed to be removed, and to simply click the mouse button to dispose of them. This was done until all CDP's with glyceryl chains of one to ten units had been created in separate files.

Connecting the glyceryl units to the cyclodextrin molecules was the next essential step. This was accomplished by selecting the Cnnct Command in the Main Button Panel. The two atoms to be connected were chosen, and then the Start Command in the Main Button Panel generated the linkage.

After the creation of all the CDP's and the guest molecules the alignment and docking processes of guest to host was done, with the bump check command. Real time torsional rotations, and real time molecular translations and rotations were also used to position the molecules. For the β-CDP and γ-

CDP pyrene was used as a guest molecule. Because pyrene is a symmetrical molecule, there was no specific end that preferred to enter the cavity. In the case of the α-CDP p-nitrophenol, and p-hydroxylmethyl benzoate were guests. In our initial studies of both of these molecules, the alcohol end was oriented so that it was facing the cavity. We refer to this as the "normal position" in the open binding conformation, and an example of this position is seen in Figure 8. Some studies using ^{13}C NMR performed by D Martin Davies at the University of Northumbria have determined that the nitro group of p-nitrophenol binds to the cavity in preference to the hydroxyl group.[16] As a result of this finding, what we term the "inverted position" in the open binding conformation was studied as well. This position occurs when the nitro or ester groups of the p-nitrophenol and p-hydroxylmethyl benzoate respectively, bind to the cavity in alpha CD or alpha CDP. Figure 9 provides a view of p-hmb binding in the inverted position to α-CDP.

The secondary view screen of the molecule (which is located in the bottom right corner of the primary view screen) contains three buttons, Rot T, TR Mol, and TR ALL. The TR Mol button's purpose is to move the guest molecule in an appropriate position that will allow for binding. Once in position, the molecule can be oriented by holding down the middle mouse button, and the x, y, or z keys for rotation in the x-axis, y-axis, or z-axis respectively.

The bump check option could be used by clicking on the Opt button in the Main Button Panel, and then the Bump Check button in the Opt menu. This

option shows "repulsive nonbonded overlaps between nearby atoms,"[17] with dotted colored lines. Blue lines illustrate the least steric hindrance, followed by green, yellow, orange, and finally red, which illustrates the greatest amount of hindrance.

After aligning the guest molecule properly, the last step before minimizing the structure was to insure that the angles in the glyceryl chain were in their lowest energy state. The Rot T button in the secondary view screen was clicked on to do this. This button allowed for the adjustment of all of the dihedral angles in the chain. Optimal values in the cyclodextrin polymers are +60°, -60°, and 180°. This process was done by choosing the Rot T command, then clicking on all of the bonds in the glyceryl chain one at a time.

When the previous steps had been completed, there were two ways in which the structure could be minimized. The first method was to minimize the structure interacting within the MacroModel program. This was done by choosing the ENRGY button in the Main Button Panel. MM2 parameters were selected, and water was chosen as a solvent by pressing the SLVNT button. After depressing the PRCG and START buttons with the primary mouse button, the minimization of the structure would commence. The PRCG button indicates the best method of minimization offered by the MacroModel program which is Polak-Ribiere conjugate gradient minimization.[18]

The second method that was used to minimize structures was as a BatchMin job that was run in the background. This was done by typing: bmin

at the % prompt in chandler within the unix shell. After typing bmin, the following was entered:

"< directoryname/filename.com > directoryname/filename.log &."[19]

For batch minimization to work properly, all of the parameters within the command or "com" file had to be adjusted to insure that they were accurate. The command file was edited by either typing "jot " in the unix shell on the SGI, or by entering the file folder on the desktop. The first six lines of the parameters were already set by doing an initial energy calculation. The seventh or "MINI" line was added to insure that both the structure and energy would be in the lowest state. The following is an example of a command file:

MMOD	0	1						
SOLV	3	1	0	0	0.0000	0.0000	0.0000	0.0000
EXNB	0	0	0	0	0.0000	0.0000	0.0000	0.0000
FFLD	1	1	0	0	1.0000	0.0000	0.0000	0.0000
READ								
ELST	1	0	0	0	0.0000	0.0000	0.0000	0.0000
MINI	1	0	500	0	0.0000	0.0000	0.0000	0.0000

The results of energy minimizations of the α, β, and γ-CDs, and CDPs were then analyzed to determine the significance of chain length for each cyclodextrin polymer. Differences between clam shell and the two open binding positions were studied, and trends for each of the three polymers were

determined. Lastly, the affinity or willingness to bind was studied for the cyclodextrins as well as the polymers.

DISCUSSION

After minimizing all structures, the calculated energies were plotted versus the glyceryl chain length. Figure 12 illustrates the trends seen in α-CDPs. This graph has six lines, representing normal open binding to p-hmb, inverted open binding to p-hmb, clam-shell binding to p-hmb, normal open binding to p-np, inverted open binding to p-np, and clam-shell binding to p-np. The significance of this figure are the trends that can be seen rather than individual energies. Keeping in mind that a lower energy value is representative of a more stable structure, it can be seen that for both p-hmb, and p-np, that the open normal or inverted binding conformations are more stable.

Figure 13 illustrates similar trends for beta CDPs. In this plot the line for the clam-shell binding data points is at all times higher in energy than the line for the open binding points. This indicates that pyrene bound to β-CDP with a glyceryl chain from one to ten linker units will always prefer the open binding conformation.

The data provided from the gamma CDP calculations was plotted to generate Figure 14. This figure like the previous two indicates that two pyrene molecules will bind to the γ-CDP in the open binding conformation in preference to clam-shell binding.

A summary of the results from the three previously mentioned figures can be seen in Table 1. The slopes, intercepts, and standard deviation of lines

shown in Figures 12-14 were obtained using Excel. The first column provides the energy in kJ/mol at the y-intercept, indicative of polymers in the hypothetical limit of zero glyceryl units. The intercept values are reference points to use when studying the remainder of the data.

The second column, which are the slopes, indicate the change in total energy with increasing linker length. The slope for α-CDP with p-hmb bound is most negative when binding occurs in the inverted open conformation. This is not in accordance with our initial assumption that the alcohol group would provide less steric hindrance in the CD, and therefore be more likely to bind than the ester group. One possible explanation for this observation could be the parameters and force field used. MM2 in MacroModel is effective when contrasting somewhat large energy differences between clam-shell and open binding data. but the difference between the normal and inverted open binding positions is significantly less substantial. The energy values generated for a CDP bound to a guest are on the order of $4x10^3$ kJ/mol; however the difference between normal and inverted binding is only 1 kJ/mol.

The slope for p-np bound to α-CDP was most negative in the inverted open conformation as well. This finding supports what Davies and Savage found in their ^{13}C NMR studies.[16] The two found that the nitro group would bind in preference to the alcohol group. Again, however, this slope is similar to that when p-np binds with α-CDP in the normal position. Because the slopes are so similar, it is once again difficult to determine exactly which position in the open binding conformation is preferable.

For beta and gamma CDP the slope values were most negative for the open binding conformation. This indicates that the open binding conformation is more stable than clam-shell for both of these polymers. There is much less strain when the polymer binds in the open conformation. For polymers to bind to a guest in the clam-shell conformation, the glyceryl chain must be bent and contorted in such a fashion so that the guest molecule is completely encapsulated by both cyclodextrin molecules. In order to do this, strain is placed on the glyceryl backbone. This was evident during the procedure which involved constructing the model. In order to obtain a clam-shell orientation, various bonds within the glyceryl chain had to have their dihedral angles altered from the optimal values of -60°, 60°, or 180°.

The final value of columns in Table 1, is a list of R^2 values for the slopes of the lines generated in Figures 12, 13, and 14. These values illustrate the precision of the aforementioned trends.

Table 2 provides energies in kJ/mol for various cyclodextrins, cyclodextrins with guests, guests alone, and unbound polymers. The values generated can be used to study the affinities between either cyclodextrins or cyclodextrin polymers, and guest molecules, the results of which can be found in Table 3.

In determining the relative affinity of a guest with either a CD, or CDP it is best to set up a reaction formula. For example:

$$E_{\text{alpha cyclodextrin}} + E_{\text{p-nitrophenol}} \Leftrightarrow E_{\text{alpha cyclodextrin bound to p-nitrophenol}}$$

-1971 kJ/mol + -8 kJ/mol $\Leftrightarrow$ -2009 kJ/mol

-1979 kJ/mol $\Leftrightarrow$ -2009 kJ/mol

Since the right side is 30 kJ/mol lower, it is more stable. As a result, p-nitrophenol will bind to α-CD in a water solvent.

These computations were performed for all CD's and CDP's in the open binding conformation. They were not performed in the clam-shell conformation, because this would require an energy value for an unbound CDP in this conformation. Since it is difficult to determine whether or not a polymer is qualitatively in the clam-shell conformation without a guest molecule present, these calculations were not performed.

Some values of interest that are provided in Table 3 include the ΔE values for the normal and inverted positions of p-np and p-hmb. For p-nitrophenol there is a lower energy value for the inverted position, as opposed to the normal position. Again, the work by Davies and Savage is supported. The opposite is seen with p-hydroxylmethyl benzoate, which has a lower ΔE in the normal position and that binding is preferable. This supports our initial proposal that the alcohol group would bind rather than the ester side chain.

In Table 3, positive values for ΔE indicate that for some guest, and cyclodextrin polymer conformations, binding should not be observed when they are in the aqueous solution. These values occur most commonly when the glyceryl linker chain has only one unit. This trend is seen in all polymers with the exception of the β-CDP, and is most likely due to the strain required to

make the polymer. When a polymer has an extremely small linker chain, which is the case when there is an n value of 1, it is difficult for the guest to bind.

There are a few other positive, and unusual values which most likely result from the molecules being trapped in local minima during minimization. When the polymers underwent the minimization process, their conformations were altered 500 times. The purpose of these 500 iterations was to make gradual changes to the molecule in an attempt to make it more stable. As a result of this process, it is possible that one of these changes took the molecule down a minimization "path" that was not optimal. Eventually the molecule could not be minimized any longer and was caught in a local minimum. If the molecule had been altered in a different fashion and gone down a different "path" it might have reached a lower energy value by the five hundredth iteration. This problem in the minimization process can and most likely does account for the discrepancy in some of the ΔE values provided in Table 3.

In summary, there were three significant findings in the research performed. The first and most important finding was that for alpha, beta, and gamma CDPs, open binding was preferable to clam shell binding when the polymer contained a glyceryl chain of one to ten units. As n, or the number of glyceryl units increased, it was apparent that clam shell binding became even more unfavorable, and that there was no optimal value of n for clam shell binding. Finally, it is important to note that in aqueous solution virtually all α,

β, and γ polymers with glyceryl lengths of one to ten units prefer to bind, rather than remain unbound in solution.

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APPENDIX OF TABLES AND FIGURES

Table 1: Table of slopes, intercepts and R^2 values for alpha, beta, and gamma CDP with glyceryl chains of one to ten units.

Polymer	*Intercept (k]/mol)*	*Slope (k]/mol*unit)*	*R^2 value*
Alpha CDP with p-hmb in the open binding conformation (normal)	-3735.7	-67.776	0.9987
Alpha CDP with p-hmb in the open binding conformation (inverted)	-3720.7	-68.715	0.9988
Alpha CDP with p-hmb in the clam shell binding conformation	-3694.3	-59.333	0.9813
Alpha CDP with p-np in the open binding conformation (normal)	-3935.3	-66.642	0.9946
Alpha CDP with p-np in the open binding conformation (inverted)	-3939.9	-66.794	0.9970
Alpha CDP with p-np in the clam shell binding conformation	-3918.5	-55.606	0.9785
Beta CDP with pyrene in the open binding conformation	-4640.2	-60.582	0.9964
Beta CDP with pyrene in the clam shell binding conformation	-4609.7	-56.776	0.9796
Gamma CDP with 2 pyrene molecules in the open binding conformation	-5286.0	-66.691	0.9946
Gamma CDP with 2 pyrene molecules in the clam shell binding conformation	-5248.9	-61.224	0.9945

Table 2: Energy values in kJ/mol for various cyclodextrins, cyclodextrin polymers, and guest molecules.

Molecule	*Energy Value (kJ/mol)*
α-CD	-1971
α-CD with p-nitrophenol (normal)	-2009
α-CD with p-hydroxylmethyl benzoate (normal)	-1808
α-CD with p-nitrophenol (inverted)	-2010
α-CD with p-hydroxylmethyl benzoate (inverted)	-1798
β-CD	-2337
β-CD with pyrene	-2333
γ-CD	-2681
γ-CD with 2 pyrene molecules	-2707
p-nitrophenol	-8
p-hydroxylmethyl benzoate	198
pyrene	60
2 pyrene molecules	65
n = 10	-679
α-CDP with n = 1	-3997
α-CDP with n = 1	-4010
α-CDP with n = 3	-4105
α-CDP with n = 4	-4145
α-CDP with n = 5	-4204
α-CDP with n = 6	-4293
α-CDP with n = 7	-4356
α-CDP with n = 8	-4458
α-CDP with n = 9	-4587
α-CDP with n = 10	-4604
β-CDP with n = 1	-4736
β-CDP with n = 1	-4672
β-CDP with n = 3	-4889
β-CDP with n = 4	-4935
β-CDP with n = 5	-4931
β-CDP with n = 6	-5016

Table 2: (continued)

β-CDP with n = 7	-5018
β-CDP with n = 8	-5170
β-CDP with n = 9	-5193
β-CDP with n = 10	-5177
γ-CDP with n = 1	-5414
γ-CDP with n = 1	-5357
γ-CDP with n = 3	-5489
γ-CDP with n = 4	-5508
γ-CDP with n = 5	-5660
γ-CDP with n = 6	-5738
γ-CDP with n = 7	-5697
γ-CDP with n = 8	-5828
γ-CDP with n = 9	-5843
γ-CDP with n = 10	-5923

Table 3: Calculated energy values, with a negative ΔE value indicating that the molecule and guest bound together is more stable than the molecule and guest separated in aqueous solution.

Molecule and Guest in Open Binding Conformation	*Molecule + Guest Energy (kJ)*	*Molecule with Guest Energy (kJ)*	*Change in Energy ΔE*
α-CD and p-np	-1979	-2009	-30
α-CD and p-hmb	-1773	-1808	-35
α-CD and p-np inverted	-1979	-2010	-31
α-CD and p-hmb inverted	-1773	-1798	-25
β-CD and pyrene	-2277	-2333	-56
γ-CD and 2pyrene molecules	-2616	-2707	-91
α-CD with n =1 and p-np	-4005	-3995	10
α-CD with n = 2 and p-np	-4018	-4066	-48
α-CD with n = 3 and p-np	-4113	-4157	-44
α-CD with n = 4 and p-np	-4153	-4201	-48
α-CD with n = 5 and p-np	-4212	-4279	-67
α-CD with n = 6 and p-np	-4301	-4310	-9

Table 3: (continued)

α-CD with n = 7 and p-np	-4364	-4399	-35
α-CD with n = 8 and p-np	-4466	-4453	13
α-CD with n = 9 and p-np	-4595	-4557	38
α-CD with n = 10 and p-np	-4612	-4601	11
α-CD with n =1 and p-hmb	-3799	-3798	1
α-CD with n = 2 and p-hmb	-3812	-3884	-72
α-CD with n = 3 and p-hmb	-3907	-3934	-27
α-CD with n = 4 and p-hmb	-3947	-4007	-60
α-CD with n = 5 and p-hmb	-4006	-4079	-73
α-CD with n = 6 and p-hmb	-4095	-4142	-47
α-CD with n = 7 and p-hmb	-4158	-4205	-47
α-CD with n = 8 and p-hmb	-4260	-4266	-6
α-CD with n = 9 and p-hmb	-4389	-4347	42
α-CD with n = 10 and p-hmb	-4406	-4423	-17
β-CD with n = 1 and pyrene	-4676	-4683	-7
β-CD with n = 2 and pyrene	-4612	-4762	-150
β-CD with n = 3 and pyrene	-4829	-4831	-2
β-CD with n = 4 and pyrene	-4875	-4891	-16
β-CD with n = 5 and pyrene	-4871	-4947	-76
β-CD with n = 6 and pyrene	-4956	-5023	-67
β-CD with n = 7 and pyrene	-4958	-5050	-92
β-CD with n = 8 and pyrene	-5110	-5121	-11
β-CD with n = 9 and pyrene	-5133	-5180	-47
β-CD with n = 10 and pyrene	-5117	-5246	-129
γ-CD with n = 1 and 2 pyrene molecules	-5349	-5323	26
γ-CD with n = 2 and 2 pyrene molecules	-5292	-5441	-149
γ-CD with n = 3 and 2 pyrene molecules	-5424	-5503	-79
γ-CD with n = 4 and 2 pyrene molecules	-5443	-5547	-104
γ-CD with n = 5 and 2 pyrene molecules	-5595	-5616	-21
γ-CD with n = 6 and 2 pyrene molecules	-5673	-5683	-10

Table 3: (continued)

γ-CD with n = 7 and 2 pyrene molecules	-5632	-5768	-136
γ-CD with n = 8 and 2 pyrene molecules	-5763	-5818	-55
γ-CD with n = 9 and 2 pyrene molecules	-5778	-5884	-106
γ-CD with n = 10 and 2 pyrene molecules	-5858	-5945	-87

Figure 1: Alpha Cyclodextrin (both front and side views).

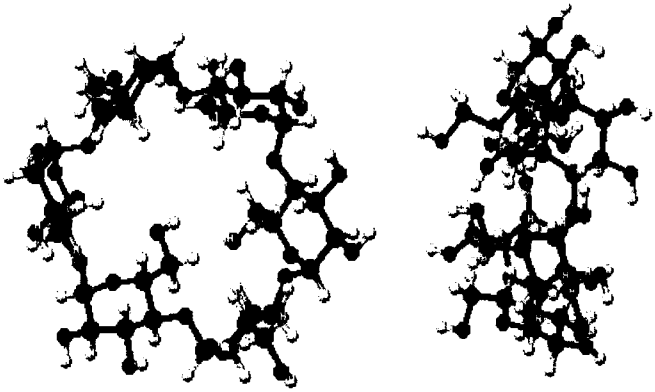

Figure 2: Beta cyclodextrin (both front and side views).

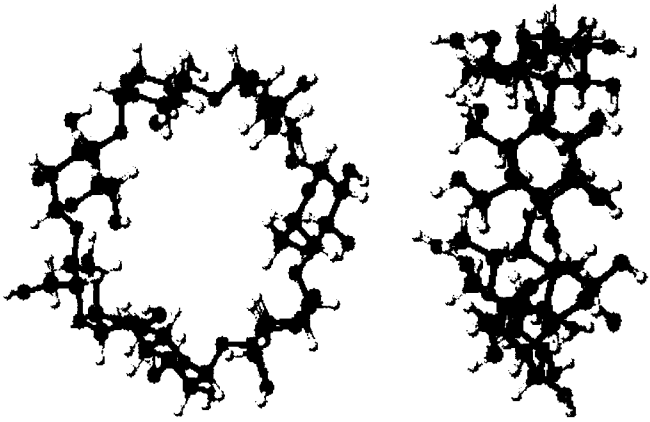

Figure 3: Gamma cyclodextrin (both front and side views).

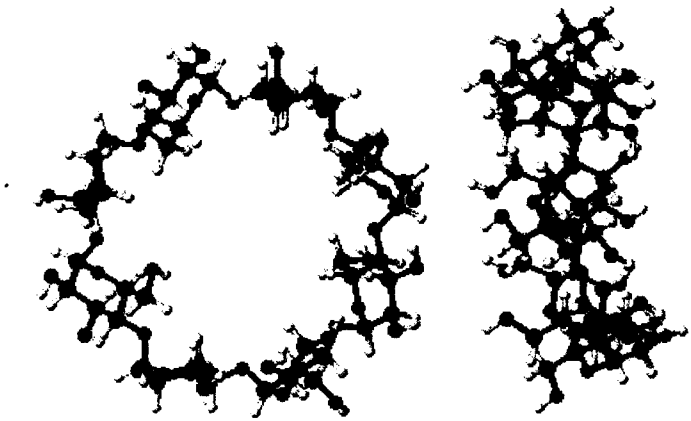

Figure 4: P-hydroxylmethyl benzoate guest molecule.

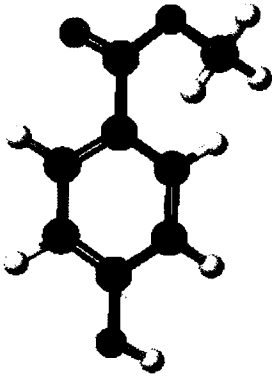

Figure 5: P-nitrophenol guest molecule.

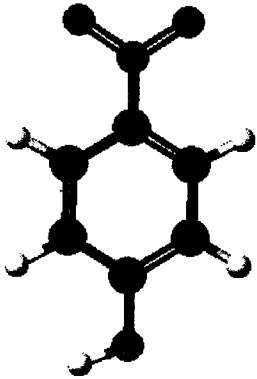

Figure 6: Pyrene guest molecule.

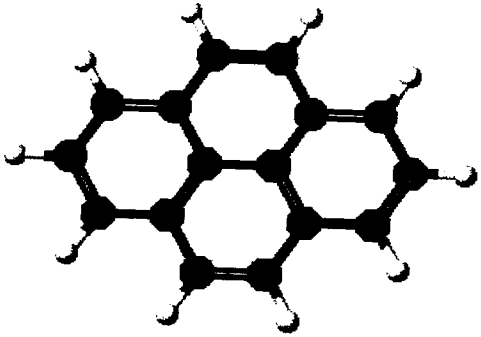

Figure 7: Glyceryl unit (n=1) where end oxygen is bound to another carbon, and end carbon is bound to another oxygen.

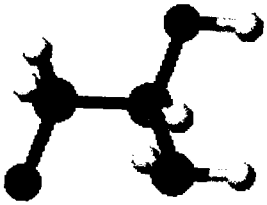

Figure 8: Alpha cyclodextrin polymer with 4 glyceryl linker units (p-hydroxylmethyl benzoate is in the open binding conformation and in the normal position).

Figure 9: Alpha cyclodextrin polymer with 4 glyceryl linker units (p-hydroxylmethyl benzoate is in the open binding conformation and in the inverted position).

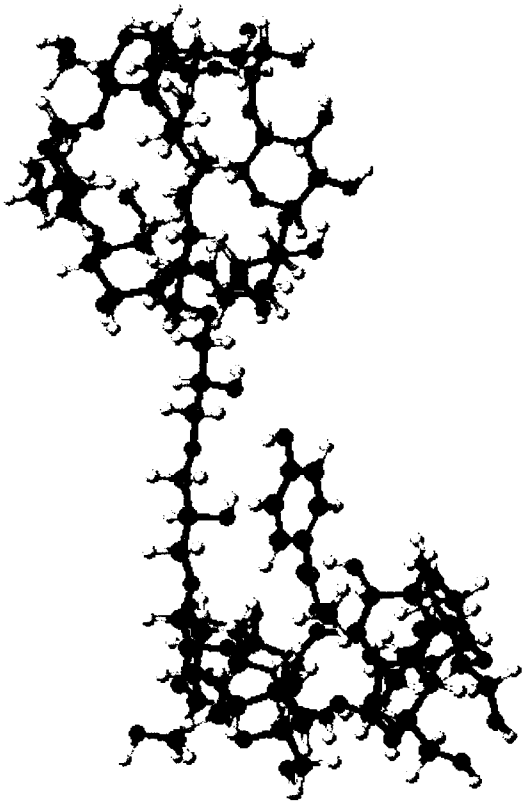

Figure 10: Beta cyclodextrin polymer with 8 glyceryl linker units (1 pyrene molecule is bound in the clam shell binding conformation).

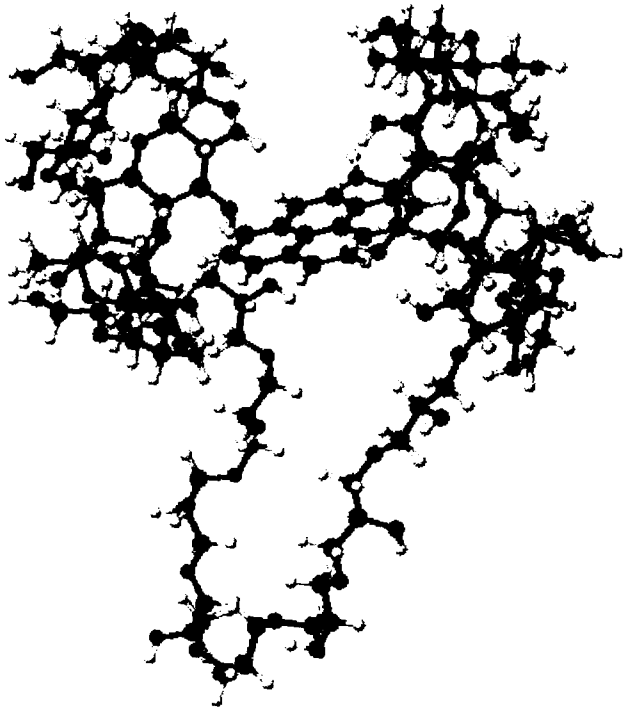

Figure 11: Gamma cyclodextrin polymer with 2 glyceryl linker units (2 pyrene molecules are bound in the clam shell binding conformation).

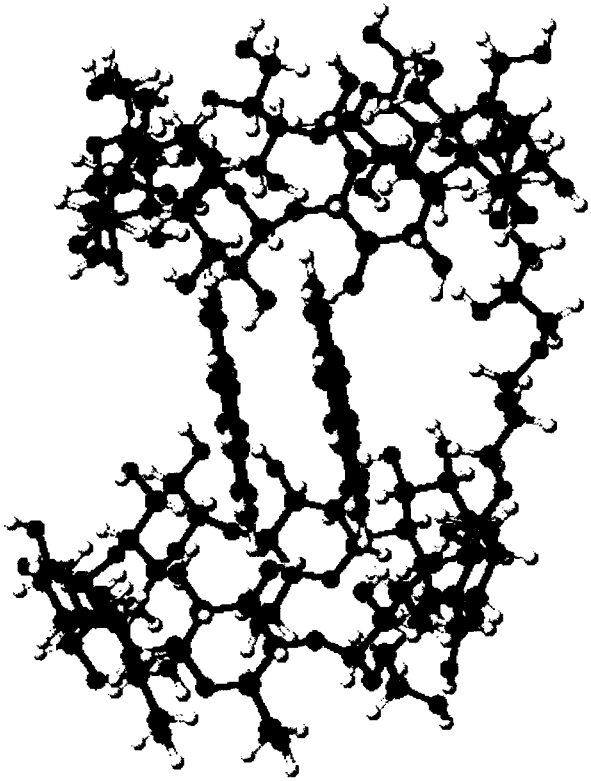

Figure 12: Plot of Minimized Energy vs. Glyceryl chain length for p-hmb, and p-np in the open, inverted, and clam shell binding conformations in alpha CDP

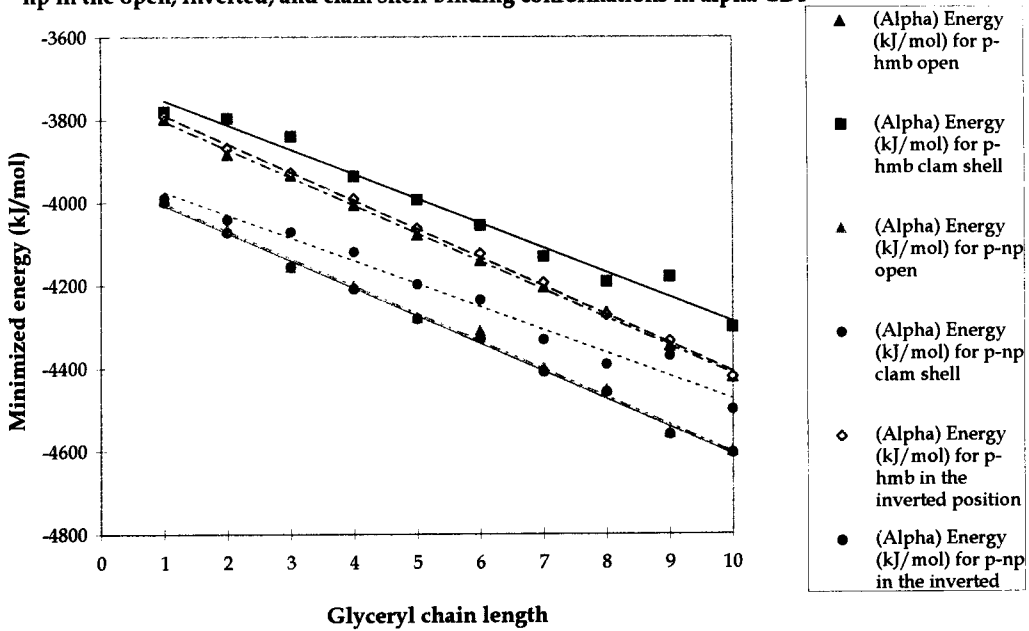

Figure 13: Plot of Minimized Energy vs. Glyceryl chain length for pyrene in the open and clam shell binding conformations in beta CDP

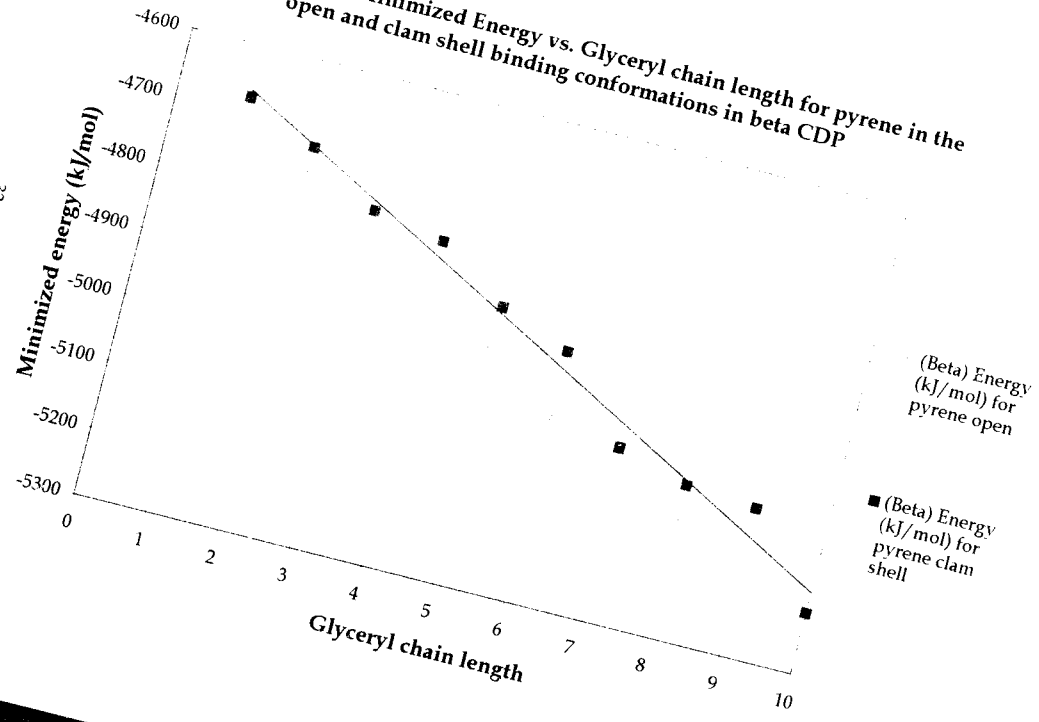

Figure 14: Plot of Minimized energy vs. Glyceryl chain length for 2 pyrene molecules in the open and clam shell binding conformation in gamma CDP