

the number of H bonds. Structures generated with the high dielectric constant process fewer H bonds than those which result when a dielectric constant of 1.5 or -1 is used.

Conclusions

The photoexcited anthraquinone moieties in 1-3 react by rapid H abstraction. In the presence of a good H-atom-donating solvent such as 2-propanol abstraction is a bimolecular process, whereas without such a solvent, the hydrogen-atom source is the CD itself. The latter process appears to be selective in that only the primary alcohols are oxidized. Furthermore, the reaction appears to be regioselective among the six possible C6-OHs. One major product could be isolated from the photolysis of 2, suggesting that one

methylene group was greatly preferred to the others for abstraction. Molecular modeling results suggest that photooxidation of the E-glucose residue is favored. Finally, these molecules would make poor hosts for photoinduced electron transfer (PET) reactions due to this self-destructive reaction which will occur in the absence of a bound guest. We are exploring the selectivity of H abstraction with other pendant groups as well as searching for better groups for PET reactions.

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Molecular Mechanics Studies on Inclusion Compounds of Cyanine Dye Monomers and Dimers in Cyclodextrin Cavities

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Abstract: Molecular mechanics calculations were applied to monomers and dimers of cyanine dyes (3,3'-diethyloxycarbocyanine iodide (DOC), 3,3'-diethyloxadicarbocyanine iodide (DODC), and 3,3'-diethyloxatricarbocyanine iodide (DOTC)) in β - and γ -cyclodextrin (CD) cavities, to explain the experimental findings that DODC and DOTC dimers are included both in β - and γ -CD cavities and that the DOC dimer is included only in a γ -CD cavity. The calculations show that the inclusion of dye dimers into cyclodextrin leads to stabilization of the total system; however, the (DOC)₂- β -CD system is much less stable than the others, in agreement with experimental findings. Except for DOC and β -CD, the dimer dye (D₂)-CD systems are found to be more stable than the corresponding monomer dye (D)-CD systems. This seemingly puzzling result can be rationalized in terms of the important role of the van der Waals stabilization energy in the inclusion compounds. The present study shows the usefulness of molecular mechanics calculations in the investigation of inclusion compounds.

Introduction

Molecular mechanics (MM) calculations have been widely used in studies of molecular structures and conformational energies.¹ The application of MM calculations to inclusion compounds, however, has been rather limited.²⁻⁷ Wipff et al.² studied alkali metal ion complexes of 18-crown-6, using the AMBER program.³ Watson et al.⁴ studied the 1:1 and 1:2 complexes formed between benzo-15-crown-5 and dithioamide or thioacetamide, respectively. Geue et al.⁵ made a conformational analysis of [111] and [222] cryptands. Dharanipragada et al.⁶ treated the design of an optically active macrocyclic host composed of diphenylmethane and 4-phenyl-1,2,3,4-tetrahydroisoquinoline units. Imashiro et al.⁷ studied the inclusion of *n*-alkanes in urea. These authors used the MM2 program.

Cyclodextrins (CDs) constitute a very important family of compounds which lead to many types of inclusion compounds which are of fundamental scientific interest and also have potential for practical applications.⁸⁻¹⁰ In an experimental study of cyanine dyes (D) complexed with β - or γ -CD (CD) in aqueous solution,^{11,12} we found that dimerization of dyes can be induced by CDs. Examination of 13 cyanine dyes with different end groups and different lengths of the linking chain, including 3,3'-diethyloxycarbocyanine iodide (DOC), 3,3'-diethyloxadicarbocyanine iodide (DODC), and 3,3'-diethyloxatricarbocyanine iodide (DOTC), (Table I in ref 12) indicated that induced dimerization by CD was governed by steric factors. As an empirical rule, dimerization

did not occur for dyes with (a) bulky end groups or bulky atoms on the linking chain and (b) short linking chains. In some cases a bulky end group that hindered induced dimerization of the dye with the short linking chain did not hinder dimerization of the dye with a longer linking chain (e.g. DOC and DODC with β -CD). These findings strongly suggested that the linking chains of a dye dimer were contained within the cavity of a CD and the end groups were located outside. The D₂-CD (2:1), not D₂-(CD)₂ (2:2), stoichiometry was found from the concentration dependence of absorbance at the wavelength of the dimer band.¹² (The structure suggested above also ruled out the D₂-(CD)₂ composition, since the linking chains of a dye dimer could not thread two CDs.) These experimental results are consistent with a structure of the inclusion compound in which a dye dimer is contained within the cavity of a CD.

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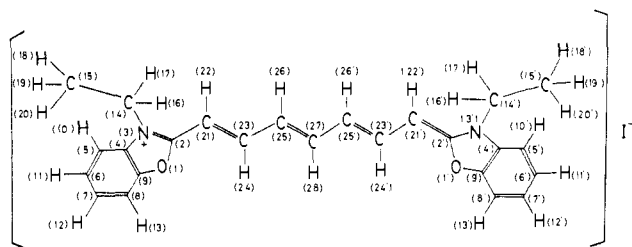


Figure 1. Structural formula of 3,3'-diethyloxatricarbocyanine iodide (DOTC).

The experiments indicated that the DODC and DOTC dimers were included in a β - and γ -CD cavity, while the DOC dimer was included only in a γ -CD cavity.^{11,12} From steric considerations, the β -CD ring should undergo some expansion when dye dimers are included in the cavity. This is energetically feasible only when the destabilization caused by the expansion of CD ring is compensated for by the stabilization due to the hydrophobic host (CD)-guest (dye) interaction and dimerization of the dye molecules. In the present paper, this aspect is investigated by MM calculations. Preliminary results have been given in preceding papers.^{11,12}

Procedure

1. General Considerations. The calculations in this paper were made with use of the MMP2 program with charge option¹³ which takes π -electron conjugation into account. The original version of the MMP2 program has been extended to include up to 400 atoms which are sufficient for the cyanine dye dimer-CD systems. The values of some parameters were determined by the aid of the MNDO method.¹⁴ The calculations did not take into account water molecules (both inside and outside the CD cavity). The principal goal of the present research is to compare the energy gain (or loss) on the formation of an inclusion compound for a series of systems composed of monomer or dimer dyes and β - or γ -CDs. It was expected that the energy gain (or loss) would be dominated by steric repulsion between the guest (dye) and the host (CD). Therefore, the relative values of energy gain (or loss) for the series on complex formation should not be critically dependent upon the presence of water molecules. The inclusion of water molecules in the calculation, however, would change the absolute values of total energy.

The potential energy functions used in the MMP2 program include the stretching, bending, torsion, stretching-bending interaction, van der Waals, and electrostatic interaction terms.^{1,13}

2. Optimized Structure of the Cyanine Dye Monomers. Three cyanine dyes, DOC, DODC, and DOTC, were considered in the present study. As an example, the structural formula of DOTC is shown in Figure 1. The optimized structures of these cyanine dye monomers were calculated by the MNDO method. The values of the unknown MM parameters around N and O atoms in the benzoxazole ring then were determined by using these structures.

3. Optimized Structure of the Host (CD Ring). Detailed X-ray diffraction data have been reported for α -¹⁵ and β -CD.¹⁶ For γ -CD¹⁷ no coordinate values have been reported although an X-ray diffraction study has been made. Therefore, the optimized structures for the CDs were obtained by MM calculations. The actual procedure was as follows. The optimized structure of an α -D-glucopyranose unit was determined by the MM method. Then the initial structure of a total CD molecule was constructed by connecting appropriate numbers of this unit by α -1,4-bonding. The total structure of the CD was then optimized by the MM calculation to include the mutual interactions between the glucopyranose units.

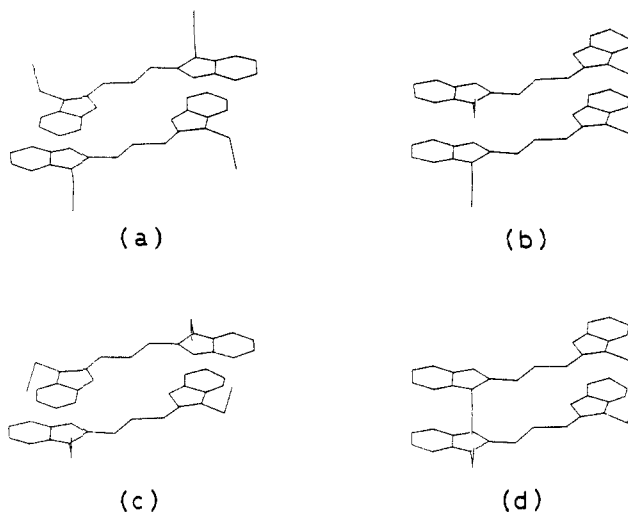
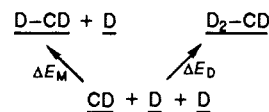


Figure 2. Four molecular arrangements of the dimer of a cyanine dye.

Scheme I



4. Optimized Structure and the Stabilization Energy of Host-Guest (Dye Monomer or Dimer) Inclusion Compounds. The optimization of dye monomer-CD and dye dimer-CD systems by the MM calculations was performed by using a dye monomer and a CD, separately optimized, as building blocks.

(a) Dye Monomer-CD Inclusion Compounds. In the starting structure of the dye monomer-CD system, the CD ring is located on the central portion of methine chain of the dye. After optimization of the total structure, the energy changes (ΔE_M) on the formation of the inclusion compound $D-CD$ were calculated as the energy difference between [dye monomer-CD (optimized)] and [dye monomer (optimized) + CD (optimized)].

(b) Dye Dimer-CD Inclusion Compounds. In choosing the starting structure of the dye dimer-CD system we have four choices in locating the two building blocks of dye monomer, schematically shown in Figure 2. The arrangement (a) with a C_2 symmetry corresponds to the most compact structure and thus causes the least steric repulsion on the formation of a host-guest inclusion compound with a CD. Therefore, this arrangement was chosen in the calculation. The initial distance between two monomer units was taken to be 3.4 Å, the "thickness" of a benzene ring. The CD ring is again located on the central portion of the methine chain of the dye, and the total system was optimized. The energy changes (ΔE_D) on the formation of the inclusion compound D_2-CD were then calculated as the energy difference between [dye dimer-CD (optimized)] and [two dye monomers (optimized one by one) + CD (optimized)].

The energy changes (ΔE_M and ΔE_D) on the formation of inclusion compounds $D-CD$ and D_2-CD , respectively, are shown in the scheme below (Scheme I). In the calculation of ΔE_M and ΔE_D , every underlined species was optimized.¹⁸

Results and Discussion

1. Force Field Parameters. The new force field parameters for bonds involving N and O atoms in the benzoxazole ring in the cyanine dye are presented in Table I. The MM structure op-

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(18) Pictures in Figure 2, parts a-d are only schematic. They do not represent the optimized structures. Actually we have not made the optimization of dye dimer by itself. We have optimized the whole system of dye dimer included in the CD cavity. The referee has suggested that the energy minimum of the dye dimer may appear when two monomers are slipped lengthwise, i.e. phenyl ring of one monomer almost above the five-membered ring of the other. In the optimized structures of the dye dimer in the CD ring, as seen in Figure 4, the benzoxazole rings of two monomers are found nearly eclipsed, because the CD ring squeezes out the bulky end groups.

Table I. Force-Field Parameters in MM Calculation Determined in this Work

Bond Stretching Constants				
bond type ^a	example ^b	k_r , mdyn Å ⁻¹	r_0 , Å	
C-N	14-3	7.500	1.474	
C'-N	2-3	10.000	1.410	
C'-O	2-1	10.000	1.370	
Angle Bending Constants				
angle type ^a	example ^b	k_θ , mdyn rad ⁻²	θ_0 , deg	
C'-N-C'	2-3-4	0.430	107.860	
C'-O-C'	2-1-9	0.670	108.720	
C'-O-L	2-1	0.350	125.640	
N-C'-O	3-2-1	0.430	109.290	
C'-N-C	2-3-14	0.595	126.550	
N-C-H	3-14-16	0.903	107.96	
N-C-C	3-14-15	0.580	113.287	
Torsional Constants (kcal mol ⁻¹)				
torsional angle type ^a	example ^b	V_1	V_2	V_3
C'-C'-N-C	21-2-3-14	-0.270	10.000	0.000
C'-N-C'-O	4-3-2-1	-0.930	8.000	0.000
C'-N-C-C	2-3-14-15	-0.440	0.240	0.060
C'-N-C-H	2-3-14-16	0.000	0.000	-0.240
N-C'-C'-O	3-4-9-1	0.000	15.000	0.000
N-C'-O-L	3-2-1	0.000	0.000	0.000
H-C-C-N	18-15-14-3	-0.150	0.000	0.150
O-C'-N-C	1-2-3-14	0.000	10.000	0.000
C'-O-C'-N	9-1-2-3	-0.930	8.000	0.000

^aDesignations are as follows: C, carbon (sp³); C', carbon (sp²); H, hydrogen; L, lone pair; N, nitrogen (sp²); O, oxygen (sp²). ^bSee Figure 1.

timized with these parameters corresponds well with the MNDO-optimized structure.

2. Quality of the Expanded Version of MMP2 Program Used in the Present Study. As a test of the quality of the "400 atom version" of the MMP2 program, the structure of α -CD (containing two water molecules in its cavity) was optimized by using the program. The bond lengths and bond angles obtained then were compared with those from X-ray analysis.¹⁵ The averaged differences in the bond lengths, 0.0022 and 0.0057 Å for C-C and C-O bond, respectively, were smaller than the standard deviations given in the X-ray analysis data. The averaged differences in the bond angles were 0.08°, 0.4°, 1°, and 3° for C-C-C, C-C-O, C-O-C, and O-C-O angles, respectively. The standard deviation reported for the experimental data was ~1°. Therefore, the "400 atom version" of the MMP2 program reproduces well the X-ray analysis data. However, there is a difference in the direction of O-H bonds of the water molecules in the α -CD cavity between the MM-optimized structure and the experimental structure. The MMP2 program did not take hydrogen bonds into account. Moreover, the calculation was made for α -CD with two water molecules in the cavity, whereas the α -CD studied by X-ray contained two water molecules in the cavity, and four water molecules outside of the cavity. From these considerations, we believe the "400 atom version" of the MMP2 program developed in this study is applicable to systems containing the CD ring.

3. Charge on the Dye Molecule. The net atomic charge on each atom in DOC, DODC, and DOTC was calculated by the MNDO method. As an example, the results for DOTC are given in Table II. A large positive charge is found on the carbon atom at the edge of benzoxazole ring (atoms no. 2 and 2', see Figure 1). The oxygen and nitrogen atoms in the benzoxazole ring (no. 1 and 1', no. 3 and 3', respectively) carry negative charges. In the usual π -electron picture of a positively charged cyanine dye, the nitrogen atom in the end chromophore is assigned a positive charge. In a calculation of π -electron system of a positively charged cryptocyanine¹⁹ the nitrogen atom does exhibit a positive charge. However, in the present MNDO calculation, the nitrogen atom

Table II. Net Atomic Charges in DOTC^a

benzoxazole ring		methine chain		ethyl group			
O(1)	-0.135	O(1')	-0.137	C(21)	-0.280	C(14)	0.175
C(2)	0.358	C(2')	0.356	C(23)	0.203	C(15)	-0.003
N(3)	-0.297	N(3')	-0.296	C(25)	-0.246	C(14')	0.175
C(4)	0.003	C(4')	0.003	C(27)	0.192	C(15')	-0.004
C(5)	-0.001	C(5')	-0.001	C(25')	-0.246	H(16)	0.035
C(6)	-0.045	C(6')	-0.045	C(23')	0.202	H(17)	0.032
C(7)	-0.028	C(7')	-0.028	C(21')	-0.279	H(18)	0.017
C(8)	-0.030	C(8')	-0.032	H(22)	0.087	H(19)	0.023
C(9)	0.024	C(9')	0.024	H(24)	0.055	H(20)	0.014
H(10)	0.096	H(10')	0.095	H(26)	0.076	H(16')	0.035
H(11)	0.084	H(11')	0.083	H(28)	0.046	H(17')	0.031
H(12)	0.083	H(12')	0.083	H(26')	0.076	H(18')	0.023
H(13)	0.086	H(13')	0.086	H(24')	0.055	H(19')	0.014
				H(22')	0.086	H(20')	0.017

^aAtoms are numbered as in Figure 1.

has a negative charge, since all the valence electrons (π , σ and lone pair) are taken into account. (Note that the charge of lone-pair electrons are assigned to the nitrogen atom.) A similar situation appears in the CNDO/2 calculation of 1,1'-diethyl-2,2'-carbocyanine chloride when all valence electrons are considered.²⁰ The positive charges on hydrogen atoms are larger on the benzoxazole ring and methine chain than those on the ethyl group. These characteristics are shared by the other two dyes (DOC and DODC).

4. Charge Distribution on the CD Ring and Its Effect on the Conformation of CD. The net atomic charge on each atom in the CD ring has been calculated by the MNDO method. The actual calculation was made for each glucopyranose unit, because of the limited size of the MNDO program used. The MM optimization of CD was then made with and without the charge option of the program. The difference in the results was found to be very small. Averaged differences in bond distances are 0.0010 and 0.0009 Å for C-C and C-O bonds, respectively, and those in bond angles are 0.005°, 0.071°, 0.276°, and 0.335° for C-C-C, C-C-O, C-O-C, and O-C-O, respectively. The dihedral angles within the glucopyranose ring and those in glucoside bonds calculated with and without the charge option almost coincide. Therefore, although the charge option has been used in the calculation of the molecular conformation of the CD ring, its use is not critical.

5. Structure and Flexibility of CD Ring. In order to study the flexibility of the CD ring, MMP2 calculations were made for several conformations of β - and γ -CD. For β -CD the MM-optimized structures were calculated for C_7 and C_1 symmetry. The latter corresponds to the CD ring incorporating a DODC monomer. For γ -CD the MM optimization was made for C_2 (two types), C_8 , C_4 , and C_1 symmetry. The structure with C_4 symmetry is close to that of the CD which enclosed a cyanine dye dimer. As examples, the C_7 structure of β -CD and C_8 structure of γ -CD are depicted in Figure 3, parts a and b. In these structures, the form of CD cavity is not a cylinder, but a truncated cone, in which the diameter is larger in the secondary hydroxy groups side than in the primary hydroxy groups side. All the D-glucopyranose units are shown to have a chair form. These findings are in line with the results of proton NMR,²¹⁻²⁵ IR,^{23,26} and ORD^{27,28} studies on CDs. The total energies (E_T s), i.e., the sum of electrostatic, van der Waals, and internal (stretching, bending, stretch-bend, and torsion) energies, for these conformations are compared in Table III.

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Table III. Total Energies and Their Decomposition into Components for Several Conformations of β -CD and γ -CD Uncomplexed (kcal mol⁻¹)

CD symmetry	β -CD		γ -CD				
	C ₁	C ₇	C ₁	C _{2(a)}	C _{2(b)}	C ₄	C ₈
E_T^a	258.8	265.7	291.3	297.5	292.3	291.3	303.6
E_{int}^b	84.4	89.8	91.0	97.2	93.1	92.3	101.9
$E(\text{stretch})$	10.7	11.5	11.5	12.6	12.0	11.9	13.3
$E(\text{bend})$	45.5	46.6	47.8	50.5	48.8	49.6	52.3
$E(\text{stretch-bend})$	5.3	5.7	5.7	6.3	5.9	5.9	6.7
$E(\text{torsion})$	22.9	26.0	26.0	27.8	26.4	24.9	29.6
E_{vdw}^c	51.0	53.4	58.1	59.4	57.5	57.0	61.3
E_{el}^d	123.4	122.5	142.2	140.9	141.7	142.0	140.4

^aTotal energy; $E_T = E_{int} + E_{vdw} + E_{el}$. ^bSum of $E(\text{stretch})$, $E(\text{bend})$, $E(\text{stretch-bend})$, and $E(\text{torsion})$. ^cTotal van der Waals energy. ^dTotal electrostatic energy.

Table IV. Changes in the Total Energies and Their Components on the Formation of Cyanine Dye Dimer-CD Inclusion Compounds (kcal mol⁻¹)

CD dye dimer	β -CD			γ -CD		
	(DOC) ₂	(DODC) ₂	(DOTC) ₂	(DOC) ₂	(DODC) ₂	(DOTC) ₂
complex						
ΔE_D^a	-18.74	-31.86	-32.72	-33.48	-37.10	-33.05
ΔE_{int}^b	18.52	7.37	4.22	7.26	0.36	-0.88
ΔE_{vdw}^c	-62.53	-63.63	-59.82	-64.30	-60.43	-54.50
ΔE_{el}^d	25.25	24.40	22.88	23.56	22.97	22.36
host(CD) ^e						
ΔE_{Dh}	14.67	10.58	7.34	4.85	2.63	1.57
$\Delta E_{int,h}$	13.69	6.71	4.45	5.18	0.60	-0.46
$\Delta E_{vdw,h}$	0.04	3.50	2.65	-0.57	2.52	2.07
$\Delta E_{el,h}$	0.94	0.36	0.23	0.24	-0.48	-0.03
guest(dye dimer) ^e						
ΔE_{Dg}	22.42	11.90	7.62	16.20	10.39	7.40
$\Delta E_{int,g}$	4.83	0.65	-0.24	2.08	-0.24	-0.19
$(\Delta E_{int}(\text{torsion}))^f$	(3.06)	(0.54)	(-0.21)	(1.93)	(0.16)	(0.14)
$\Delta E_{vdw,g}$	-12.74	-16.74	-18.93	-16.51	-17.77	-19.25
$\Delta E_{el,g}$	30.33	27.98	26.79	30.53	28.40	26.84
interaction of host-guest ^e						
ΔE_{Di}	-55.83	-54.35	-47.68	-54.53	-50.13	-41.76
$\Delta E_{vdw,i}$	-49.82	-50.40	-43.55	-47.32	-45.18	-37.32
$\Delta E_{el,i}$	-6.01	-3.95	-4.13	-7.21	-4.95	-4.44

^aChanges in the total energy, i.e., (total energy of the inclusion compound D₂-CD) - [2(total energy of D) + (total energy of CD)]. ΔE_D values are decomposed into components as $\Delta E_D = \Delta E_{int} + \Delta E_{vdw} + \Delta E_{el} = \Delta E_{Dh} + \Delta E_{Dg} + \Delta E_{Di}$. ^{b-d}Internal, van der Waals, and electrostatic component of ΔE_D , respectively. ^eSubscripts h, g, and i indicates host (CD), guest (dye dimer), and host-guest interaction, respectively. ^fTorsional component included in $\Delta E_{int,g}$.

Examination of Table III shows that the difference in steric energy of these conformations is about 10 kcal mol⁻¹, showing the flexibility of the CD ring. In other words, the energy difference between the β -CD conformers or the γ -CD conformers is very small.

6. Optimized Structures of Inclusion Compounds and Total Energy Changes on the Formation of Inclusion Compounds. (a) **Cyanine Dimer-CD Inclusion Compounds.** The optimized structures of cyanine dye dimer-CD inclusion compounds (D₂-CD) are given in Figure 4, parts a-c, with (DOC)₂, (DODC)₂, and (DOTC)₂- β -CD as examples. The total energy changes (ΔE_D s) on the formation of these inclusion compounds from their respective components (two Ds and one CD, each of these three separately optimized) are given in the top line of Table IV. (In the other lines in the table, the decomposition of ΔE_D values into the host, guest, and their interaction components is given. ΔE_{Dh} is the energy change for the host (CD) optimized in the D₂-CD system compared to the host optimized by itself. ΔE_{Dg} is the energy change for the guest (a dye dimer, D₂) optimized in the D₂-CD system compared to two monomers (D) optimized by themselves. ΔE_{Di} is the difference between the total energy of D₂-CD and the sum of total energies of "CD optimized in D₂-CD" and "D₂ optimized in D₂-CD". The decomposition of ΔE_D , ΔE_{Dh} , ΔE_{Dg} , and ΔE_{Di} values into the internal, van der Waals, and electrostatic components allows one to assess the main factors in the stabilization of inclusion compounds.) All pairs show negative ΔE_D values which correspond to stabilization on the formation of the inclusion compounds. However, the ΔE_D of (DOC)₂- β -CD is much less negative than the other pairs. This pair is characterized by a severe deformation of the guest (dye dimer) (see

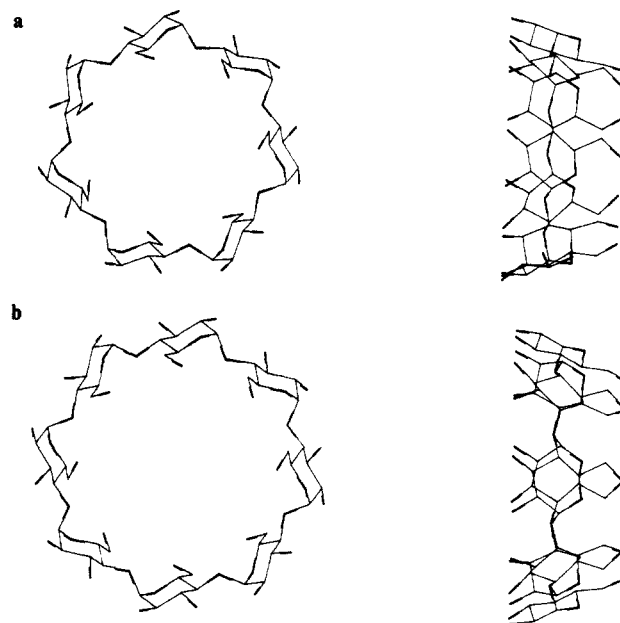
**Figure 3.** Optimized structure of (a) β -CD with a C₇ symmetry, and (b) γ -CD with a C₈ symmetry.

Figure 4a), in contrast to the other two pairs in which the dye dimer assumes a conformation with the two dye molecules arranged face to face. This leads to a large value of ΔE_{Dg} and the

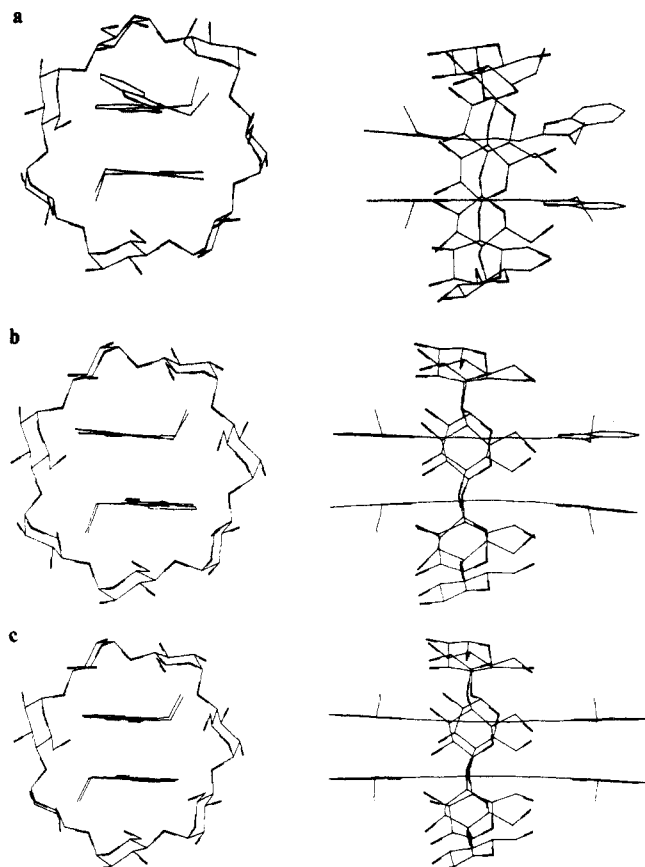


Figure 4. Optimized structure of (a) $(\text{DOC})_2\text{-}\beta\text{-CD}$, (b) $(\text{DODC})_2\text{-}\beta\text{-CD}$, and (c) $(\text{DOTC})_2\text{-}\beta\text{-CD}$.

ΔE_D value is less negative than for the other pairs. This is in agreement with the experiments on aqueous solutions of cyanine dye-CD systems which show that $\text{DOC-}\beta\text{-CD}$ is the only pair among the six pairs for which the dye dimer is not included in the CD cavity.^{11,12} Two additional factors must be taken into account when one considers the formation of an inclusion compound in aqueous solutions. Even if the dye dimer-CD system is stable when the central methine chain of the dye is included in the CD cavity with the bulky end chromophore located outside, the steric hindrance in the course of the inclusion process may inhibit the formation of the system. As shown later (section 8), the $(\text{DOTC})_2\text{-}\beta\text{-CD}$ pair must overcome a potential barrier in order to accommodate the second dye monomer. The barrier is higher for the $(\text{DODC})_2\text{-}\beta\text{-CD}$ pair. The barrier height of $(\text{DOC})_2\text{-}\beta\text{-CD}$ pair (not calculated) should be even higher. The other factor to be considered is the presence of water. In aqueous solution, the cavities of free CDs are filled with water molecules, and the CD-water interactions stabilize the system. The inclusion of dye molecules occurs at the expense of this stabilization. Therefore, the introduction of water molecules should lead to some shift in the ΔE_D values to the positive (i.e. unstable) side. These factors may explain the failure of $(\text{DOC})_2\text{-}\beta\text{-CD}$ formation in aqueous solution.

(b) **Cyanine Monomer-CD Inclusion Compounds and Comparison with the Dimer Inclusion Compounds.** Table V shows the total energy changes (ΔE_M s) on the formation of each monomer dye- β - (or γ -)CD inclusion compound (D-CD). All six pairs show negative ΔE_M s (i.e. stabilization). It should be noted that the total energy changes for $\text{D}_2\text{-CDs}$ (ΔE_D values in Table IV) are more negative (i.e. indicative of a more stable structure) than those of corresponding D-CDs (ΔE_M values in Table V), with the $\text{DOC-}\beta\text{-CD}$ case as the only exception. This is the only pair which does not show experimentally the inclusion of dye dimer.^{11,12} For the other pairs the MM calculation shows that dimer inclusion compounds are more stable than the corresponding monomer compounds. At first sight this is difficult to interpret considering the large volume of dimer dye compared to the monomer dye.

Table V. Changes in the Total Energies on the Formation of Cyanine Dye Monomer-CD Inclusion Compounds (ΔE_M) and the Difference in the Total Energy Changes on the Formation of Dimer Dye-CD and Monomer Dye-CD Inclusion Compounds from the Respective Constituents ($\Delta E_D - \Delta E_M$)

CD dye monomer	$\beta\text{-CD}$			$\gamma\text{-CD}$		
	DOC	DODC	DOTC	DOC	DODC	DOTC
complex						
ΔE_M^a	-29.28	-27.97	-22.44	-23.63	-20.53	-16.04
ΔE_{Mh}	3.57	1.54	1.60	1.97	0.57	0.46
ΔE_{Mg}	0.27	0.47	0.55	0.43	0.34	0.37
ΔE_{Mi}	-33.12	-29.97	-24.58	-26.02	-21.45	-16.87
$\Delta E_D - \Delta E_M^b$	10.54	-3.89	-10.28	-9.85	-16.57	-17.01

^aChanges in the total energy, i.e., (total energy of cyanine dye monomer-CD inclusion compound D-CD) - [(total energy of D) + (total energy of CD)]. The ΔE_M values are decomposed into the host (h), guest (g), and the interaction (i) components ($\Delta E_M = \Delta E_{Mh} + \Delta E_{Mg} + \Delta E_{Mi}$). ^bDifferences in the total energy changes on the formation of dimer dye-CD and monomer dye-CD inclusion compounds from the respective constituents (ΔE_D in Table IV and ΔE_M in this table, respectively).

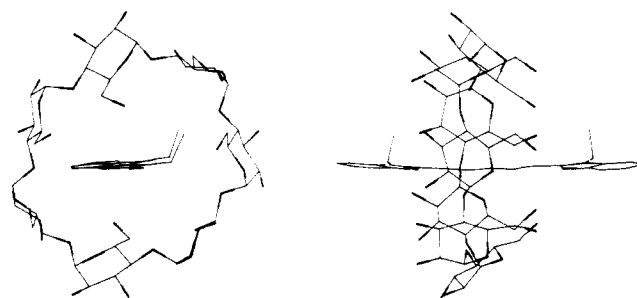


Figure 5. Optimized structure of DODC (monomer)- $\beta\text{-CD}$.

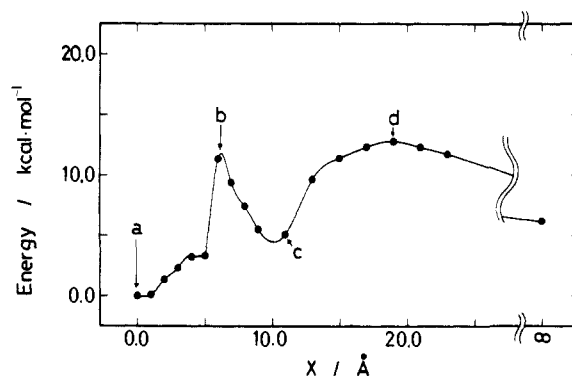


Figure 6. Potential energy change along the path of inclusion $(\text{DOTC-}\beta\text{-CD}) + \text{DOTC} \rightarrow (\text{DOTC})_2\text{-}\beta\text{-CD}$.

However, there is experimental evidence that $\text{D}_2\text{-CD}$ is more stable than D-CD. In an experiment on the $(\text{DODC})_2\text{-}\beta\text{-CD}$ system the absorbance at the wavelength of the dimer band was measured and its dependence on the total concentration of the dye was simulated by considering the two-step equilibria between $(2\text{D} + 2\text{CD})$, $2(\text{D-CD})$, and $(\text{D}_2\text{-CD} + \text{CD})$.¹² It was shown that the concentration of D-CD should be very small compared to that of $\text{D}_2\text{-CD}$.¹² The smaller stability of D-CD compared to $\text{D}_2\text{-CD}$ is probably due to the presence of large empty spaces between the dye monomers and the interior surface of the CD cavities, as shown for $\text{DODC-}\beta\text{-CD}$ in Figure 5, leading to smaller van der Waals stabilization energies between host and guest.

7. **Origin of Stabilization of Dimer Dye-CD Inclusion Compounds.** In this section we consider the various factors which stabilize the dye-CD inclusion compounds.

(a) **van der Waals Interactions between the Host and the Guest.** The stabilization energy due to these interactions is rather large, 40-50 kcal mol⁻¹ ($\Delta E_{vdw,i}$ in Table IV). The van der Waals interaction arises from the sum of London's dispersion forces between all nonbonded atom pairs in the inclusion compound. The large interaction energies thus are attributed to the close proximity

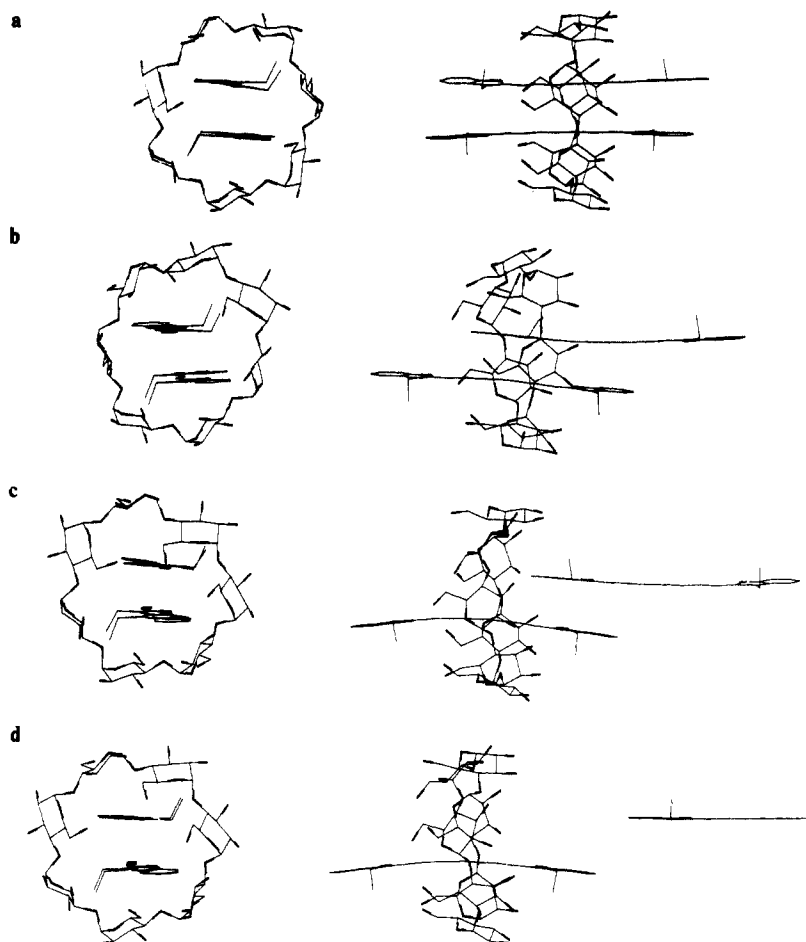


Figure 7. Optimized structure of $(\text{DOTC})_2\text{-}\beta\text{-CD}$ system along the path of inclusion; a–d correspond to points indicated in Figure 6.

between the outer surfaces of the guests (dye dimers) and the interior wall of the host (CD). The inner diameters of CD cavities are 7.0 and 8.4 Å for $\beta\text{-CD}$ and $\gamma\text{-CD}$, respectively.⁸ The experimental data in ref 29 show that small guest molecules do not fill the cavities and van der Waals stabilization is decreased.

(b) Electrostatic Interaction between the Host and the Guest. Our calculations show that stabilization due to the electrostatic interactions between hosts and guests is about 4–7 kcal mol⁻¹ (Table IV ($\Delta E_{\text{el},i}$)). This shows that the electrostatic interaction plays some role in the stabilization of inclusion compounds containing charged species such as cyanine dye molecules. (In the presence of polar water molecules, the stabilization may be reduced to some extent, however.)

(c) Dimerization of Cyanine Dyes. In the present calculation, the formation of a cyanine dimer from the constituent monomers leads to stabilization (ΔE_{Dg} in Table IV, for example, 7.62 kcal mol⁻¹ for DOTC), which is a result of the electrostatic repulsion between two positively charged dye monomers ($\Delta E_{\text{el},g}$ in Table IV, 26.79 kcal mol⁻¹ for DOTC). If water molecules were introduced into the calculations, some stabilization might be obtained. Taking $(\text{DOTC})_2$ as an example, the corresponding electrostatic interaction energy, 26.79 kcal mol⁻¹ (Table IV) reduces to 3.80 kcal mol⁻¹ in water ($d = 10.66$). The total energy of $(\text{DOTC})_2$ in water can be estimated to be the sum of this value and the van der Waals interaction (-18.93 kcal mol⁻¹) to be -15.13 kcal mol⁻¹. The minus sign indicates stabilization. This value of stabilization energy is comparable to the -20.8 kcal mol⁻¹ which is the dimerization energy in water of 3,3'-diethylthiatricarbocyanine *p*-toluenesulfonate.³⁰

The stabilization of the inclusion compound therefore is due primarily to van der Waals interaction between the host and guest (this explains the larger stabilization of $\text{D}_2\text{-CD}$ than D-CD).

Electrostatic host–guest interactions and dimerization of the dye (in the presence of water) also contribute to the stabilization of dimer dye–CD inclusion compounds.

8. Structural and Energy Changes along the Inclusion Pathway. As mentioned in section 6a, another key factor in the formation of inclusion compound is the heights of the energy barriers during the inclusion process. The energy change in the reaction



was calculated along the reaction path.³¹ The actual calculation was made in the reverse direction i.e., for the dissociation of one of the DOTC molecules, using the MM2, not the MMP2, program.³² One of the two DOTC molecules in the $\beta\text{-CD}$ cavity was pulled away parallel to the center axis which threads the CD ring (the *x*-axis), while the other molecule remained near the original position. The full optimization allowing the displacement of the remaining dye molecule in the *y* and/or *z* direction was not made. The energy of the total system (two dye molecules plus CD ring) is shown in Figure 6. The optimized structures at points a–d are shown in Figure 7. Two potential barriers were found. The broader one at $x \geq 11$ Å corresponds to the passage of the large end group of the dye across the mouth of the CD ring and is due to the large strain in the CD ring. The second, a sharp and higher barrier near $x = 7$ Å, can be attributed to the larger strain of the CD ring and an additional strain in the DOTC molecule due to the forced rotation of an ethyl group, which passes near the central part of the CD ring at this point. The barrier height of about 12 kcal mol⁻¹ appears to be small enough for the dye molecule

(31) Note that the present work is intended to explain the experimental findings in the conditions that essentially no dye dimers are present in the solution. Therefore, it is natural to consider a two-step mechanism, in which a CD takes one dye molecule at a time.

(32) The MM2 program (without π -electron conjugation) is used here due to problems in implementing the MMP2 program.

(29) Cramer, F.; Henglein, F. M. *Chem. Ber.* **1957**, *90*, 2561.

(30) West, W.; Pearce, S. J. *Phys. Chem.* **1965**, *69*, 1894.

to surmount. Moreover, our calculations without the full optimization overestimate the barrier height. The primary hydroxy groups on the glucopyranose unit turn inward to fill the empty space formerly occupied by one DOTC molecule, and this yields a strain in the CD ring higher than in the fully optimized monomer inclusion compound. The calculation on the (DODC)₂-β-CD system also gives two potential barriers. The height of the second, higher, barrier is rather large (42 kcal mol⁻¹) in this case. This is due to the shorter methine chain in DODC compared to DOTC which forces the CD ring to deform more severely than in the DOTC case. However, the actual barrier height must be much smaller than calculated, because the inclusion of the DODC dimer as well as the DOTC dimer in a β-CD cavity occurs experimentally.^{11,12} The dye molecule remaining in the CD cavity must make some displacement in the y and/or z direction which would reduce the barrier height. A full optimization with such displacements should result in a smaller barrier height.

Conclusions

Molecular mechanics calculations are applied to inclusion compounds formed by cyanine dye monomers or dimers and β- or γ-CD. These calculations account for the stabilization of the total system by the inclusion process and explain why the (DOC)₂-β-CD system is much less stable than other systems. This result is in accordance with the experimental studies which find that the DODC and DOTC dimers are included in both β- and γ-CD cavities, whereas the DOC dimer is included only in a γ-CD cavity. The calculations show that the dimer dye-CD (D₂-CD) system is more stable than the corresponding monomer dye-CD (D-CD) system, except for the case of DOC and β-CD. This feature is rationalized by noting that the van der Waals stabilization energy is larger in the D₂-CD system where the atomic pair distances between the guest and host are smaller than in the D-CD case. Among many factors which influence the energetics of inclusion, the van der Waals interaction dominates in the

stabilization. Electrostatic guest-host interactions and dimerization of the dye play additional roles.

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Supplementary Material Available: Procedure for the determination of MM force-field parameters of cyanine dyes; a table on the comparison of bond lengths and bond angles of the MMP2-optimized and MNDO-optimized structures of DOC, DODC, and DOTC; figures on the structure of α-CD dihydrate ((H₂O)₂ inclusion compound) optimized by the MMP2 calculation (with and without the charge option) and the experimental structure (data from ref 15) of α-CD hexahydrate for comparison; tables on the comparison of bond lengths, bond angles, and dihedral angles of the MMP2-optimized (with and without the charge option) and experimental (from ref 15) structures of α-CD; tables of net atomic charges of DOC and DODC; figures of optimized geometry of β-CD and γ-CD with several different symmetries; figures of the optimized geometry of (DOC)₂⁻, (DODC)₂⁻, (DOTC)₂-γ-CD, DOC⁻, DOTC-β-CD, DOC⁻, DODC⁻, and DOTC-γ-CD inclusion compounds (29 pages). Ordering information is given on any current masthead page.

Thermal Rearrangements of Allenes. Synthesis and Mechanism of Cycloaromatization of π and Heteroatom Bridged Diallenes¹

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Abstract: The synthesis and thermal rearrangement of several π and heteroatom bridged diallenes has been investigated. *o*-Diallenylbenzenes **5**, **14**, **24** and bis(γ,γ-dimethylallenyl) ether **8** were prepared by addition of dibromocarbene to the corresponding divinyl precursor, followed by treatment of the resulting dibromocyclopropane derivative with methyllithium. Bis(γ,γ-dimethylallenyl) sulfide **10** was generated by reaction of (γ,γ-dimethylallenyl)lithium with sulfur dichloride, while the corresponding selenides **12** and **16** were synthesized by an S_N2' reaction of sodium selenide with α,α-dimethylpropargyl bromide. All diallenes prepared display a remarkable thermal reactivity and undergo a facile cycloaromatization. Gentle heating of diallenes **5**, **14**, **12**, and **16** gave the naphthalene derivatives **6** and **15** and selenophene derivatives **13** and **17**, respectively, in practically quantitative yields. Diallenes **8**, **10**, and **24** underwent spontaneous cyclization during preparation yielding furan **9**, thiophene **11**, and naphtho[*b*]cyclobutane **25**, respectively. A kinetic study of the rearrangement and measurement of the kinetic isotope effect using diallenes **5**, **14**, **12**, and **16**, revealed that the cyclization is a two-step process. The first and rate-determining step is an electrocyclic reaction yielding as intermediates ω-xylylenes **20** and **21**, while the second and more rapid step entails a [1,5]hydrogen transfer.

Allenenes, the simplest and best studied of all cumulenes, have reached their 100th anniversary.^{2,3} One of the best studied and

most useful reactions of allenenes is their thermal dimerization to 1,2-dimethylenecyclobutanes.⁴ The central mechanistic question