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A theoretical study on the inclusion complexation of cyclodextrins with radical cations and anions

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epoc ABSTRACT: PM3 and B3LYP/3-21G(d) calculations were performed on the inclusion complexation of cyclodextrins (CD) with radical ions. The calculations reproduced the experimental observations that the complexation of α-CD with 1,4-dicyanobenzene was weaker than with its radical anion, and that the complexation of β-CD with phenothiazine was weaker than with its radical cation. On the other hand, calculations showed that the complexation of α-CD with *p*-nitrophenolate was stronger than with its radical anion and the complexation of β-CD with viologen was stronger than with its radical cation. The different magnitudes of the interactions between the charged species and CD or water were proposed to cause such behaviors. Copyright © 2001 John Wiley & Sons, Ltd.
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KEYWORDS: cyclodextrin; radical cation; radical anion; molecular recognition; PM3; DFT

INTRODUCTION

Cyclodextrins (CDs) form inclusion complexes with various compounds in water,[1] and studies on CD complexation are important for the understanding of non-covalent interactions.[2] Among the many substrates of CD, radical ions are especially interesting.[3–13] These species are usually unstable, but some of them can be dramatically stabilized by CD in water and thus act as intermediates in certain CD-mediated reactions. Therefore, the CD–radical ion complexation provides important insights into the interplay between molecular recognition and redox chemistry,[14] and studies on it are beneficial for both the understanding of enzymatic radical ion chemistry and the design of novel molecular devices.[15]

However, experimental studies on CD–radical ion complexes remain difficult, and it is unsettled as to why the radicals can be incorporated into the hydrophobic CD cavity when they are charged. So far, the relatively well-studied CD–radical ion systems include the α-CD complexes of *p*-nitrophenolate[5] and dicyanobenzene radical anions,[6] and the β-CD complexes of viologen[10] and phenothiazine radical cation.[11,12] Interestingly, on the one hand, though the binding constant K_a of the α-CD–*p*-nitrophenolate radical anion complex is 125 times smaller than that of α-CD–*p*-nitrophenolate, the K_a of the α-CD–1,4-dicyanobenzene radical anion complex is 45 times larger than that of α-CD–1,4-dicyanobenzene. On the other hand, though the K_a of the β-CD–viologen complex is over 100 times larger than that of β-CD–viologen radical cation, the K_a of the β-CD–10-methylphenothiazine complex is 35 times smaller than that of β-CD–10-methylphenothiazine radical cation. This controversial behavior remains to be explained.

Herein, we performed a theoretical study on the above problem. Owing to the difficulty of molecular mechanical methods in dealing with radicals, semiempirical PM3 and density functional theory (DFT) B3LYP/3-21G(d) methods were used.[16]

METHODS

All calculations were performed with GAUSSIAN 98.[17] The α- and β-CDs were built and optimized by PM3 from the crystal structures.[18] The glycosidic oxygen atoms of CD were placed onto the *XY* plane and their center was defined as the center of the coordination system. The primary hydroxyl groups were placed pointing toward the positive *Z* axis.

The longer dimension of the substrate was initially placed onto the *Z* axis. The position of the substrate was defined by the *Z* coordinate of one selected atom of the substrate. The inclusion process was simulated by putting the substrate at one end of the CD and then letting it pass through the CD cavity in steps.[19] In every step, the geometry of the host–guest complex was completely

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optimized by PM3 without any restriction. Frequency calculations using PM3 were performed, which confirmed that every optimized structure was a true minimum. Finally, DFT single-point calculation at the level of B3LYP/3-21G(d) was performed on all the PM3-optimized species, both *in vacuo* and in water solution by using the Onsager continuum solvation model based on the self-consistent reaction field (SCRF) method.

RESULTS AND DISCUSSIONS

β-CD–viologen systems

Graphic representation of the energy changes involved in the inclusion process produces three curves, one each for the neutral, radical cation, and dication forms of viologen (Fig. 1). The PM3-optimized host–guest molecular structures of the three forms at each energy minimum are shown in Fig. 2, whose corresponding energies are summarized in Table 1.

According to Table 1, β-CD is indeed able to form a stable complex with viologen in each of its oxidation states in vacuum. However, in vacuum, the complex stability is found to be in the order dication $>$ radical cation $>$ neutral, according to either PM3 or B3LYP/3-21G(d) results, in contrast to the experimental observations. This result can be rationalized in terms of Morokuma energy decomposition analysis.[20] According to the theory, four types of interaction contribute to the formation of a supermolecule: (a) electrostatic interaction between permanent charges and dipoles; (b) polarization interaction, favored by large volume and polarizability of the molecules; (c) exchange energy, or Pauli repulsion; and (d) charge-transfer interaction, caused by the mixing of the filled orbitals of one component molecule with the vacant orbitals of the other. Apparently, increase of charge on viologen favors the first, second, and fourth types of interaction, resulting in a larger complexation energy.

Thus, the stronger binding of β-CD with less charged viologen in water must be caused by the solvation effect. Unfortunately, the B3LYP/3-21G(d) SCRF calculations in water indicate that the complex stability is still in the order dication $>$ radical cation $>$ neutral (Table 1). Therefore, the continuum solvation model might be questionable in modeling CD complexation in solution. In fact, the failure of the continuum solvation model in the study of supramolecular or biochemical systems has also been mentioned somewhere else recently.[21]

Therefore, it appears that an explicit solvation model should be used here. In other words, viologens form complexes with water molecules (in the first hydration shell), which may affect the binding strength between viologens and CD. Herein, four water molecules are chosen[22] to create the first hydration sphere around the viologen molecules. Owing to the problem of multiple

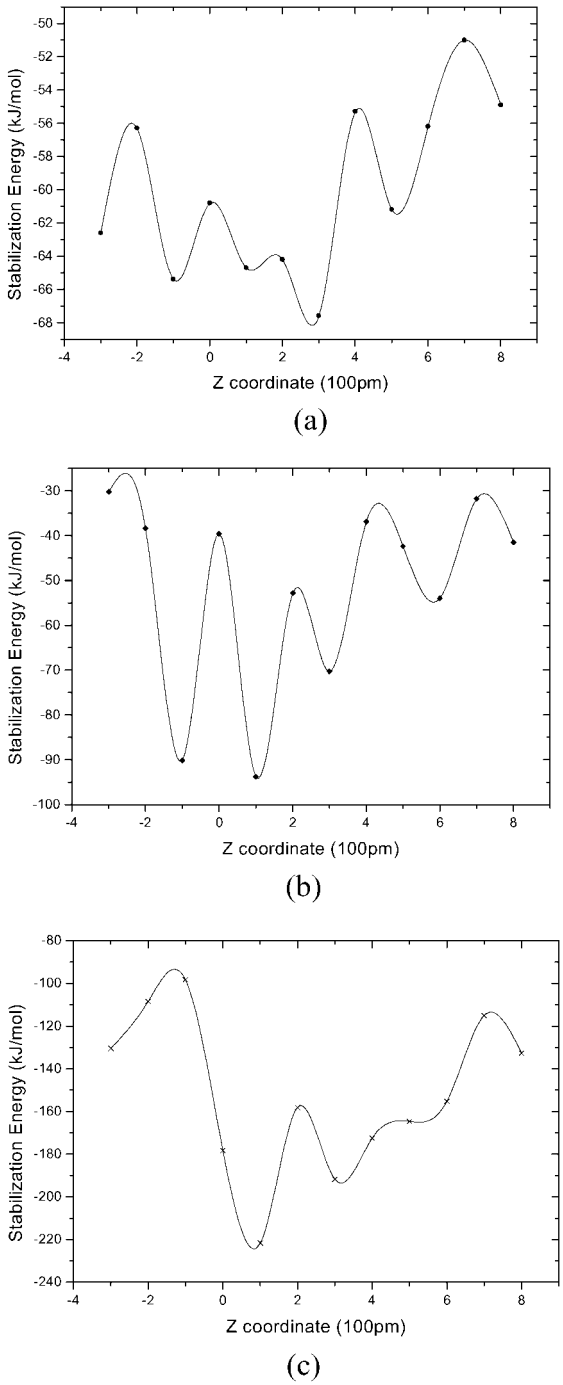

Figure 1. Graphic diagrams for the simulation of the inclusion complexation of viologen into β-CD. The position of the guest was determined by the *Z* coordinate of one nitrogen atom in the viologen from the center of the glycosidic oxygen atoms. (a) Neutral viologen. (b) Viologen radical cation. (c) Viologen dication

minima in optimization,[23] the relative geometries of the four water molecules to the substrate are not optimized but fixed, i.e. the water molecules are placed so that their dipoles point away from the major axis of the substrate (Fig. 3). The distance from the oxygen atom of the water molecule to the major axis of the substrate is also fixed at

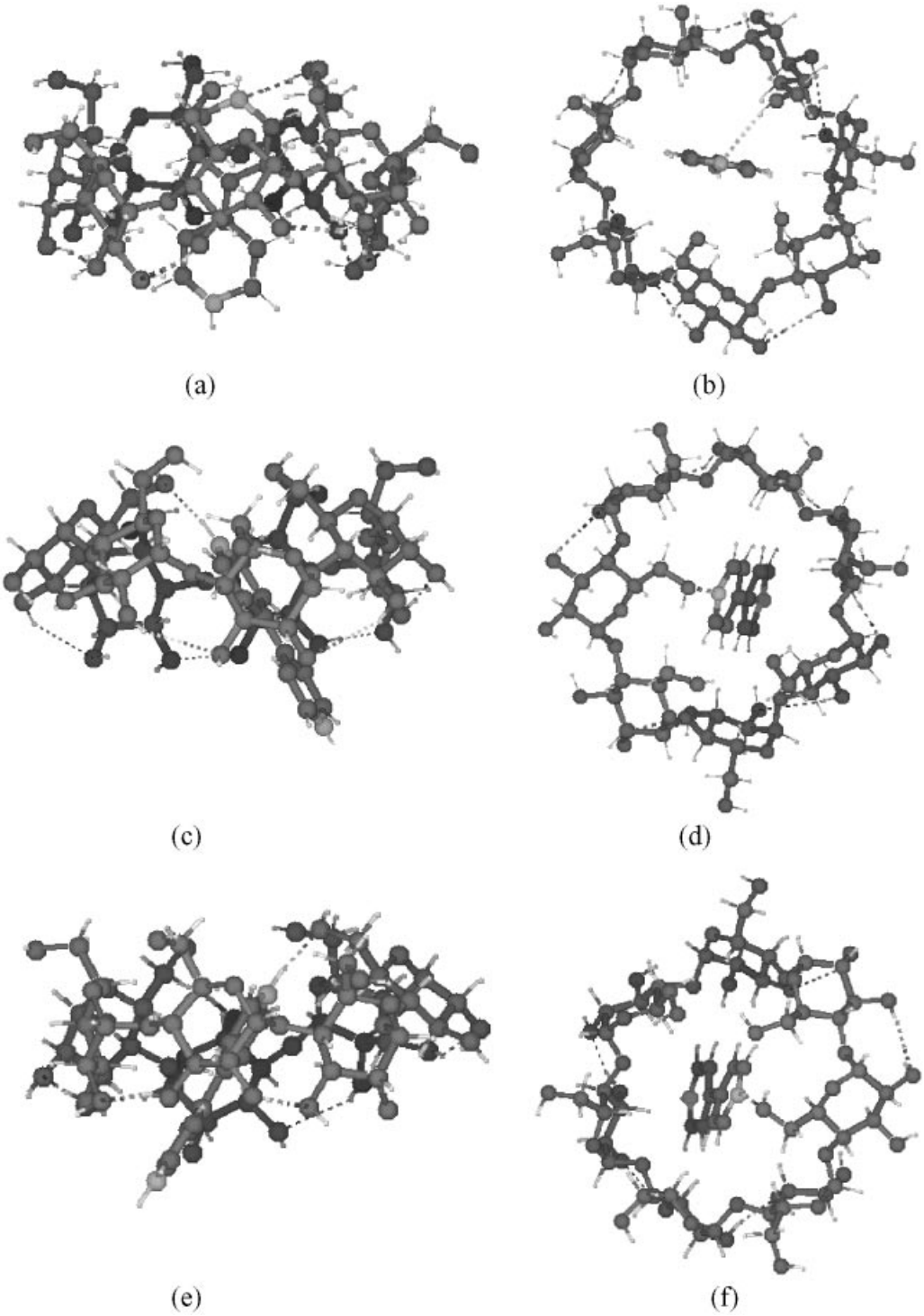

Figure 2. PM3-optimized structures of the β-CD–viologen complexes. (a) Neutral viologen, side view. (b) Neutral viologen, top view. (c) Viologen radical cation, side view. (d) Viologen radical cation, top view. (e) Viologen dication, side view. (f) Viologen dication, top view

270 pm. The energies of the viologen–water complexes are calculated with PM3 and B3LYP/3-21G(d) methods (see Table 1). As can be seen, the dication–water complex is indeed more stable than the radical cation complex and, in turn, the neutral complex. More interestingly, the difference between the complexation energy of viologen with β-CD and with water $(\Delta E_{\mathrm{CD}}^{\mathrm{vacuum}} - \Delta E_{\mathrm{water}}^{\mathrm{vacuum}})$ is more negative for the less charged viologen, indicating that the process of breaking the viologen–water complex and then forming a viologen–β-CD complex is energetically more favorable for a less charged viologen.

Table 1. Total energies of the β-CD–viologen complexes and the water–viologen systems

	Energy (kJ/mol^{-1})					
	PM3			B3LYP/3-21G(d)		
Species	Neutral	Radical cation	Dication	Neutral	Radical cation	Dication
In vacuum						
Viologen	311.3	847.6	1825.1	−1 295 218.6	−1 294 779.8	−1 293 869.2
β-CD		−6082.8			−11 151 691.6	
β-CD complex	−5839.1	−5329.0	−4479.4	−12 446 932.6	−12 446 565.3	−12 445 807.6
Stabilization energy upon complexation ΔE_{CD}^{vacuum}	−67.6	−93.8	−221.7	−22.4	−94.0	−246.9
In water						
Viologen	–	–	–	−1 295 218.6	−1 294 779.8	−1 293 869.2
β-CD		–			−11 151 692.7	
β-CD complex	–	–	–	−12 446 934.2	−12 446 572.4	−12 445 819.2
Stabilization energy upon complexation $\Delta E_{water}^{solution}$	–	–	–	−22.9	−99.9	−257.3
In vacuum						
Four waters		−893.5			−797 080.7	
Water–guest system	−371.1	107.5	946.3	−2 092 040.4	−2 091 733.5	−2 091 075.1
Stabilization energy upon complexation $\Delta E_{water}^{vacuum}$	211.1	153.4	14.7	258.9	127.0	−125.3
$\Delta E_{CD}^{vacuum} - \Delta E_{water}^{vacuum}$	−278.7	−247.2	−236.4	−281.3	−221.0	−121.6

In short, the stronger complexation between less charged viologen and β-CD in water does not mean that the gas-phase interaction between the less charged viologen and β-CD is stronger. The substrate–water interactions also play an important role in determining the order of the complexation strength, which, however, cannot be described properly with the continuum solvation model. Though the fixation of the structures of the viologen–water complexes does not accurately describe the actual hydration, it at least provides the correct information, i.e. the process of breaking the viologen–water complex and then forming the viologen–β-CD complex is energetically more favorable for a less charged viologen.

β-CD–phenothiazine systems

Similar calculations on the complexation of β-CD with phenothiazine and its radical cation give the complexa-

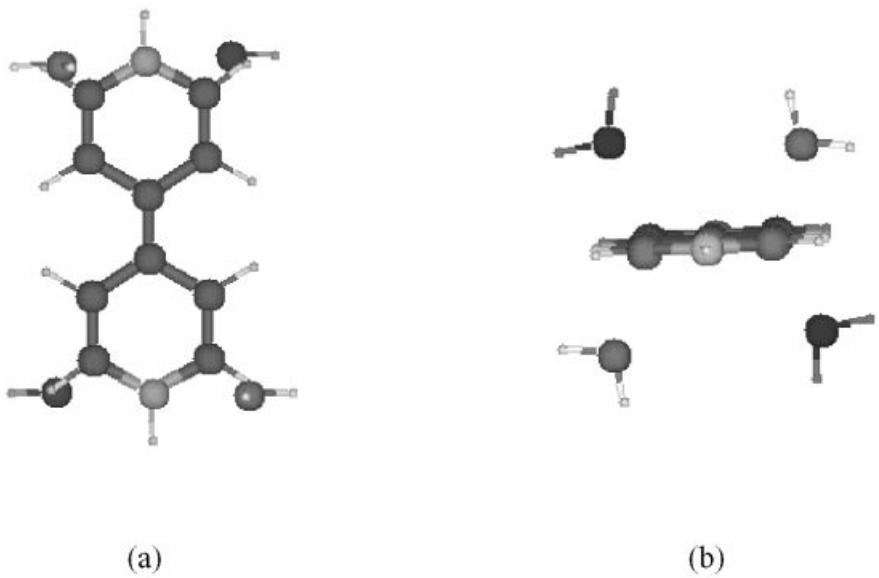

Figure 3. The water–viologen complex

Table 2. Energy aspects of the β-CD–phenothiazine complexation

	Method	Energy (kJ mol^{-1}) Neutral	Radical cation
ΔE_{CD}^{vacuum}	PM3	−49.2	−91.0
	B3LYP/3-21G(d)	−10.9	−99.6
$\Delta E_{water}^{vacuum}$	PM3	206.6	192.6
	B3LYP/3-21G(d)	247.0	169.2
$\Delta E_{CD}^{vacuum} - \Delta E_{water}^{vacuum}$	PM3	−255.8	−283.6
	B3LYP/3-21G(d)	−257.9	−268.8

Table 3. Energy aspects of the α-CD–*p*-nitrophenolate complexation

	Method	Energy (kJ mol^{-1}) Anion	Radical anion
ΔE_{CD}^{vacuum}	PM3	−81.2	−295.2
	B3LYP/3-21G(d)	−96.8	−343.6
$\Delta E_{water}^{vacuum}$	PM3	291.3	59.0
	B3LYP/3-21G(d)	58.1	−208.2
$\Delta E_{CD}^{vacuum} - \Delta E_{water}^{vacuum}$	PM3	−372.5	−354.2
	B3LYP/3-21G(d)	−154.9	−135.4

tion structures (see supporting information) and energies (see Table 2). As can be seen, the β-CD–phenothiazine radical cation complex is more stable than the neutral complex in vacuum. With the same explicit solvation model, the water–phenothiazine radical cation complex is also found to be more stable than the neutral complex.

However, here ($\Delta E_{CD}^{vacuum} - \Delta E_{water}^{vacuum}$) is less negative for the neutral phenothiazine. Thus, the process of breaking the phenothiazine–water complex and then forming a phenothiazine–β-CD complex is energetically more favorable for a phenothiazine radical cation, which agrees with the experimental observation.

α-CD–*p*-nitrophenolate systems

In contrast to viologen and phenothiazine, *p*-nitrophenolate or its radical anion when complexed with CD has two possible orientations in the host cavity. In one orientation the NO_2 group points toward the narrower α-CD rim, and this orientation is termed NO_{2endo}. In the other orientation the NO_2 group points toward the wider α-CD rim, and this orientation is called NO_{2exo}. Both orientations are considered in the PM3 optimization, and for each orientation a curve of complexation energy is obtained (see supporting information). Herein, the calculation indicates that the NO_{2endo} orientation is more favorable in energy than NO_{2exo} for *p*-nitrophenolate and for its radical anion.

The energies of the complexation with α-CD and with water are summarized in Table 3. It should be mentioned that here the water molecules are placed so that their dipoles pointed towards the major axis of the substrate (Fig. 4). The distance from the oxygen atom of the water molecule to the major axis of the substrate is also fixed at 270 pm. According to Table 3, ($\Delta E_{CD}^{vacuum} - \Delta E_{water}^{vacuum}$) is more negative for the less charged *p*-nitrophenolate. Thus, the process of breaking the *p*-nitrophenolate–water complex and then forming a *p*-nitrophenolate–α-CD complex is energetically more favorable for the less charged *p*-nitrophenolate, which agrees with the experimental observation.

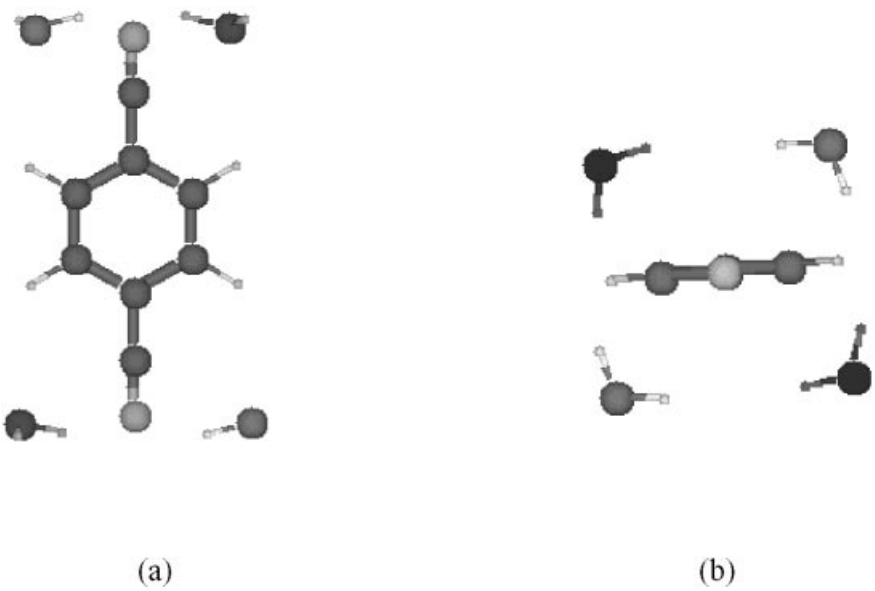

Figure 4. The water–dicyanobenzene complex

Table 4. Energy aspects of the α-CD–dicyanobenzene complexation

		Energy (kJ mol^{-1})	
	Method	Neutral	Radical anion
ΔE_{CD}^{vacuum}	PM3	−34.0	−74.3
	B3LYP/3-21G(d)	−25.1	−112.6
$\Delta E_{water}^{vacuum}$	PM3	−0.9	−36.1
	B3LYP/3-21G(d)	−67.7	−113.3
$\Delta E_{CD}^{vacuum} - \Delta E_{water}^{vacuum}$	PM3	−33.1	−38.2
	B3LYP/3-21G(d)	42.6	0.7

α-CD–dicyanobenzene systems

With the same procedure as mentioned for α-CD–*p*-nitrophenolate systems, the energies of the α-CD–dicyanobenzene complex and water–dicyanobenzene complex are obtained. The result, listed in Table 4, indicates that the stronger complexation of α-CD with the dicyanobenzene radical anion is due to the stronger interaction between α-CD and the radical anion.

Semi-continuum solvation model calculations

All of the above-mentioned energy changes ($\Delta E_{CD}^{vacuum} - \Delta E_{water}^{vacuum}$) are calculated in vacuum. However, it was recently suggested that a semi-continuum solvation model should give a better description of the solvation effect.[24] According to the model the species with its first solvation sphere should be treated with the continuum solvation model, which presumably combines the effects of bulk solvent with the local interaction between solute and solvent.

Herein, the energy changes from the water complexes to CD complexes are also obtained from B3LYP/3-21G(d) SCRF calculations in water, and the results ($\Delta E_{CD}^{aq} - \Delta E_{water}^{aq}$) are summarized in Table 5. According to Table 5, it is obvious that the results from the semi-continuum solvation calculations agree qualitatively with all the conclusions drawn from the gas-phase calculations mentioned above. Therefore, it is the first solvation sphere that plays the major role in determining the stabilities of the CD cation/anion complexes.

Table 5. Energy aspects of the CD complexation calculated with the semi-continuum solvation model

System	$\Delta E_{CD}^{aq} - \Delta E_{water}^{aq}$ (kJ mol^{-1})
β-CD–neutral viologen	−323.5
β-CD–viologen radical cation	−267.9
β-CD–viologen dication	−173.8
β-CD–neutral phenothiazine	−297.2
β-CD–phenothiazine radical cation	−318.1
α-CD–*p*-nitrophenolate anion	−196.5
α-CD–*p*-nitrophenolate radical anion	−175.7
α-CD–neutral dicyanobenzene	1.2
α-CD–dicyanobenzene radical anion	−31.5

Summary

Several valuable conclusions can be drawn from the above calculations.

(1) The calculation of CD complexation in the gas phase is not sufficient to describe the real processes occurring in solution. For the four radical ion systems, the complexation energy in the gas phase is always larger for the more charged substrate, which obviously cannot be used to interpret the experimental observations.
(2) Unfortunately, a simple continuum solvation model is not sufficient to model CD complexation in solution. In comparison, a crude explicit solvation model, at least qualitatively, indicates that the weaker complexation between CD and more charged viologen and *p*-nitrophenolate is caused by the stronger interaction between the more charged substrate and water molecules. Moreover, it appears that the affinity of a charged organic molecule to CD might be stronger or weaker than that to water, depending on the structure and electron distribution of the organic molecule. Thus, the simple concept of a hydrophobic (or hydrophilic) effect should be used with caution under such conditions.
(3) The study suggests that supramolecular systems can either stabilize or destabilize radical ions. This fact might be used in the design of some delicate molecular devices that are electrochemically controllable. Also, it appears that enzymes can either facilitate or disturb a reaction pathway by constructing certain microscopic environments for the radical ion intermediates. Therefore, there remains much to be discovered, investigated, and used in the field of supramolecular radical ion chemistry.

Supporting information

Figures of all the energy profiles of the CD complexation and figures of all the PM3-optimized CD complexes are available from the epoc website at http://www.wiley.com/epoc

Acknowledgements

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