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Crystal Structures of Two Molecular Complexes between Cationic Surfactants and Hydroquinone Showing a Melanogenesis Inhibitory Effect

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Hydroquinone, showing a melanogenesis inhibitory effect, formed crystalline molecular complexes with two cationic surfactants of benzyl(hexadecyl)dimethylammonium chloride and ethyl(hexadecyl)dimethylammonium bromide from an methanol solution at low temperatures, lower than 15 °C. The crystal structures were analyzed by X-rays at 223 K. There are two crystallographically independent hydroquinone molecules and one surfactant molecule in each crystal. One of the hydroquinone molecules is sandwiched by the surfactant molecules and makes a "common packing pattern," which has been observed in complex crystals between aromatic compounds and surfactant molecules. Another hydroquinone occupies an inversion center surrounded by the benzyldimethylammonium or ethyldimethylammonium moiety of the surfactant molecule. Such a close packing makes hydroquinone in the molecular complex stable in open air at room temperature.

The aromatic compounds make crystalline molecular complexes with a variety of surfactants, such as octadecyl-, hexadecyl-, tetradecyl-, or dodecyltrimethylammonium halides from a solubilized solution.[1,2] The crystal structures analyzed by X-rays have a similar packing pattern, which is called a common packing pattern.[3,4] An aromatic molecule is sandwiched by the alkyl groups of the surfactant molecules in the packing pattern. When a complex with this packing pattern is formed, the aromatic compound becomes thermally stable and difficult to be oxidized.[5–7]

One of aromatic compounds, hydroquinone, is well known to dermatologists as a drug of skin pigmentation, and has been used clinically.[8–10] However, hydroquinone is very easily oxidized and colored.[11] We tried to stabilize hydroquinone by making complexes with various surfactant molecules containing quaternary ammonium salts, such as alkyltrimethylammonium halides, benzyl(alkyl)dimethylammonium chloride, and ethyl(hexadecyl)dimethylammonium bromide. After many trials, two suitable complex crystals for X-ray analysis were formed with benzyl(hexadecyl)dimethylammonium chloride and ethyl(hexadecyl)dimethylammonium bromide, as shown in Scheme 1. In the present paper, the stabilization mechanism is discussed based on the crystal structures analyzed by X-rays.

Experimental

Preparation of a Complex Crystals. Cationic surfactants, benzyl(hexadecyl)dimethylammonium chloride (abbreviated as CDBAC) and ethyl(hexadecyl)dimethylammonium bromide (abbreviated as CDEAB), were purchased from Tokyo Kasei Co. Ltd. The aromatic compound, hydroquinone (abbreviated as HQ), was purchased from Wako Co. Ltd. Complex crystals were obtained from a solubilized alcohol solution in which the surfactant and the hydroquinone were solved in a molar ratio of 1:1. The complex formation was confirmed by the ultraviolet spectra. The two complex crystals, CDBAC/HQ and CDEAB/HQ, are needle and plate-like, respectively.

Crystal Structure Analysis. The cell dimensions and intensity data were obtained using the R-AXIS RAPID (Rigaku) and AFC-7R (Rigaku) at 223 K equipped with the Rigaku low-temperature apparatus for CDBAC/HQ and CDEAB/HQ, respectively. Mo Kα radiation monochromated by graphite was used. The crystal data and experimental details are listed in Table 1. The structures were solved by a direct method with the programs SIR-97[12] and SHELXS-97,[13] respectively, and were refined by a full-matrix least-squares method with the program SHELXL-97.[14] The non-hydrogen atoms were refined with anisotropic temperature factors. The HQ molecule at the center of symmetry in the crystal of CDEAB/HQ is disordered at two positions. The two positions of the disordered HQ and their occupancy factors were refined. The ratio of the two positions was refined to 50:50 within the experimental error. The two hydrogen atoms of the OH groups of HQ molecules in CDEAB/HQ appeared in the difference map, and were refined with the isotropic temperature factors. The positions of the other hydrogen were calculated geometrically. Atomic-scattering factors were taken from International Tables for Crystallography.[15] The weighting scheme was $1/[\sigma^2(F_o{}^2) + (ap)^2 + bp]$, where $p = (F_o{}^2 + 2F_c{}^2)/3$. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Copies can be obtained on request, free of charge, by quoting the publication citation and the deposition numbers (256873 and 256874).

Stability of the Surfactant Complexes against the Oxygen.

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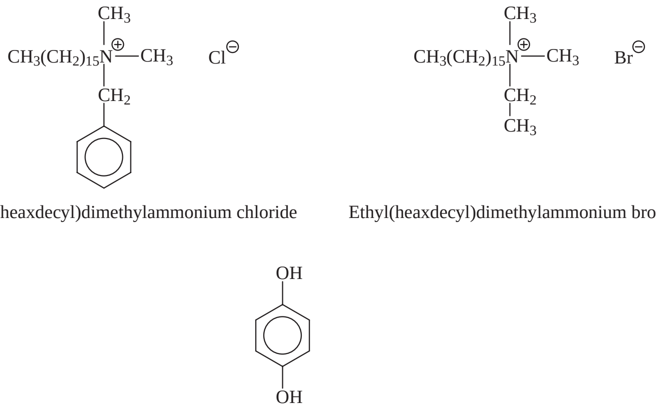
Benzyl(heaxdecyl)dimethylammonium chloride

Ethyl(heaxdecyl)dimethylammonium bromide

Hydroquinone

Scheme 1. Chemical structures of surfactants and hydroquinone.

Table 1. Crystal and Experimental Data

Complex	CDBAC/HQ	CDEAB/HQ
Formula	$C_{25}H_{46}NCl/1.5C_6H_6O_2$	$C_{20}H_{44}NBr/1.5C_6H_6O_2$
Formula weight	561.24	543.63
Wavelength/Å	0.71069	0.71069
Crystal system	monoclinic	triclinic
Space group	$C2/c$	$P\bar{1}$
Z	8	2
a/Å	18.3719(5)	9.862(3)
b/Å	7.0309(2)	23.547(8)
c/Å	50.6482(13)	7.125(2)
α/deg		93.86(3)
β/deg	91.117(1)	110.72(2)
γ/deg		80.09(2)
V/Å^3	6541.0(3)	1524.3(8)
D_x/g cm^{-3}	1.140	1.184
Absorption coefficient/mm^{-1}	0.149	1.376
$F(000)$	2456	586
Crystal size/mm	0.40 × 0.10 × 0.07	0.20 × 0.20 × 0.18
Theta range for data collection	0.80 to 27.48 deg	2.53 to 27.51 deg
Range of h	$-23 \rightarrow 23$	$-12 \rightarrow 11$
Range of k	$-9 \rightarrow 8$	$-30 \rightarrow 30$
Range of l	$-65 \rightarrow 65$	$-5 \rightarrow 9$
Reflections collection	48209	8456
Independent reflection	7487 ($R_{\text{int}} = 0.1819$)	6932 ($R_{\text{int}} = 0.0261$)
Goodness of fit on F^2	1.030	1.017
No. of refined parameters	518	298
Weighting parameters		
a	0.0845	0.0616
b	2.195	2.87
$R(I > 2\sigma)$	0.0725	0.0491
$wR(F^2)$	0.1765	0.1337
$\delta\rho/e$ Å^{-3}	+0.283, −0.351	+0.511, −0.464

Powdery specimens of the two complexes and hydroquinone alone were sieved using screens from 48 to 80 mesh, and were used in an experiment involving air exposure. The specimens were put at 37 °C in an incubator under an open condition. The decay of hydroquinone within definite time intervals was followed by a change in the UV spectra of the methanol solution at a specified wavelength for hydroquinone (291.0 nm). The decay amount was estimated by comparing the absorbance of the sample with that of a same sample without air exposure.

The Stability of the Surfactant Complexes against Light Exposure. Powdery specimens of the complexes and hydroquinone alone were prepared in the same way as before. Each specimen was put into a polyethylene bag in a vacuum and irradiated with a xenon lamp at 25 °C. The light quanta was 30 mW cm^{-2}. The decay of each sample within definite time intervals due to light exposure was followed by measuring the change in the UV spectra in the same way as before.

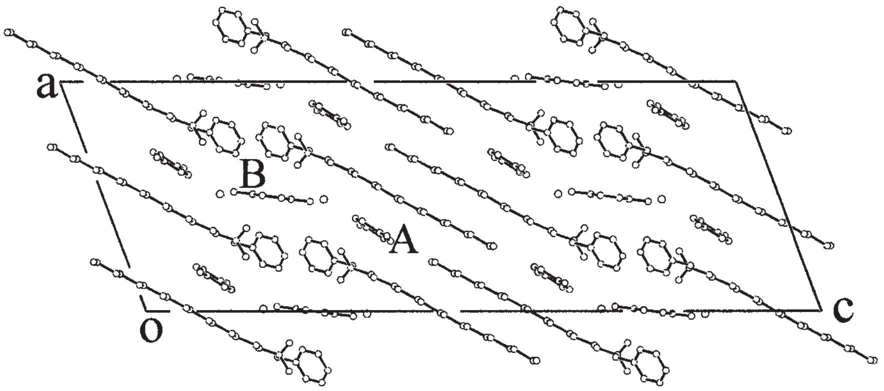

Fig. 1. Crystal structure of CDBAC/HQ viewed along the *b* axis.

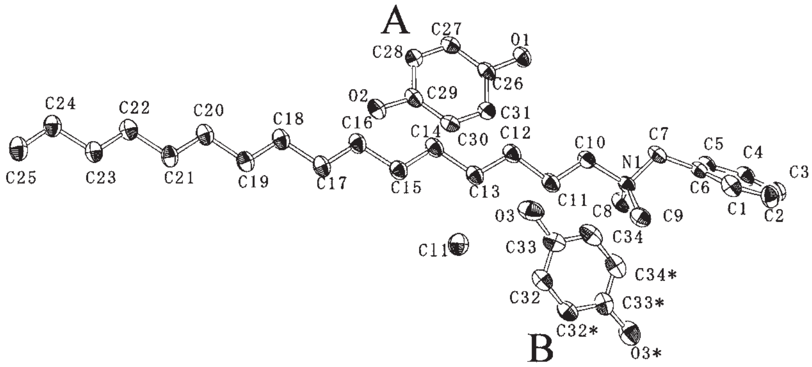

Fig. 2. Molecular structures of two CDBAC and HQ with the atomic numbering. The thermal ellipsoids are shown with 50% probability.

Results and Discussion

Crystal and Molecular Structure of CDBAC/HQ. The crystal structure viewed along the *b* axis is shown in Fig. 1. The complex is composed of one CDBAC and one and a half HQ molecules (A- and B-HQ, respectively) in an asymmetric unit. The molecular structures with the atomic numbering are shown in Fig. 2. The A- and B-HQ molecules have two OH groups with a *cis* conformation. The A-HQ molecule is sandwiched by the two CDBAC molecules in the crystal structure. Such a packing is called a "common packing pattern," which has been observed in related complexes between aromatic compounds and surfactants. One of the two OH groups of A-HQ makes a hydrogen bond with the O atom of the OH group of the neighboring A-HQ molecule to form a linear chain along the *b* axis. The acceptor OH group of A makes a hydrogen bond with the Cl anion. The hydrogen bonding pattern is shown in Fig. 3(a) and the distances of the hydrogen bonds are 2.673(3) Å (O2···O1) and 2.966(2) Å (O1···Cl1). The B-HQ molecule occupies the two-fold axis between the cationic and anionic moieties of the surfactant molecules, and also makes hydrogen bonds with the Cl anions to form a linear chain along the *c* axis. The hydrogen-bonding pattern is shown in Fig. 3(b) and the distance is 3.097(2) Å (O3···Cl1). The conformation of the hexadecyl group of CDBAC is all-trans, as observed in the related surfactant molecule. The bond distances and angles of the CDBAC and HQ molecules are not significantly different from the corresponding ones of the related surfactant molecules and HQ reported so far.

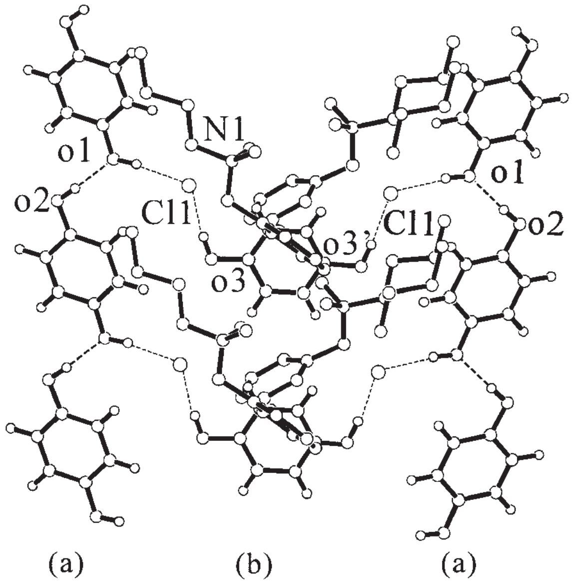

Fig. 3. Hydrogen bonds in the CDBAC/HQ complex (a) between HQ molecules in common packing pattern and (b) between HQ molecules on the two-fold axis and HQ molecules in common packing pattern.

Crystal and Molecular Structure of CDEAB/HQ. The crystal structure viewed along the *a* and *c* axes are shown in Figs. 4 and 5. The molecular structures with the atomic numbering are shown in Fig. 6. The complex is also composed of

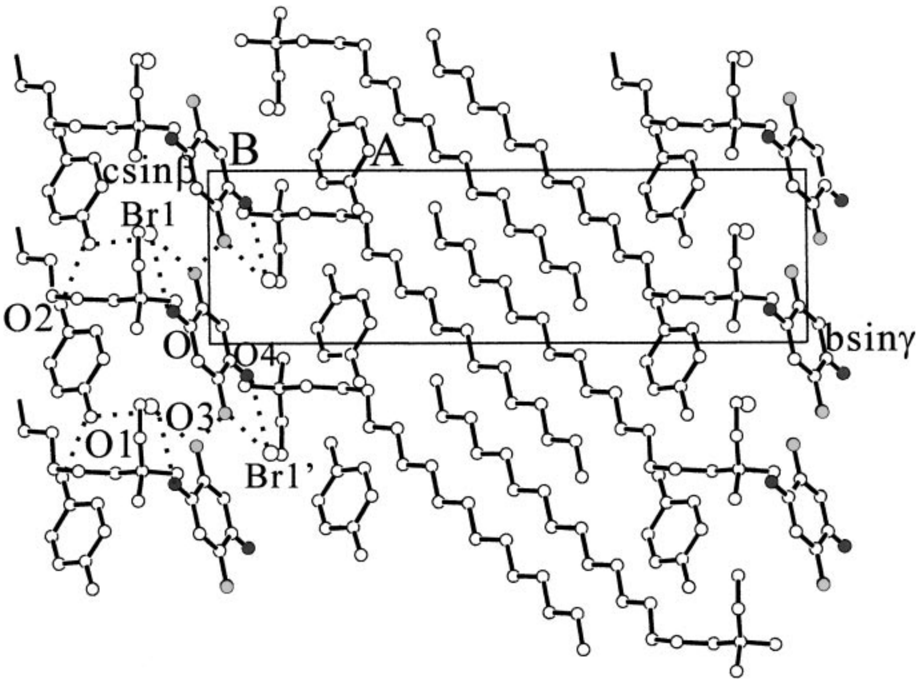

Fig. 4. Crystal structure of CDEAB/HQ viewed along the *a* axis.

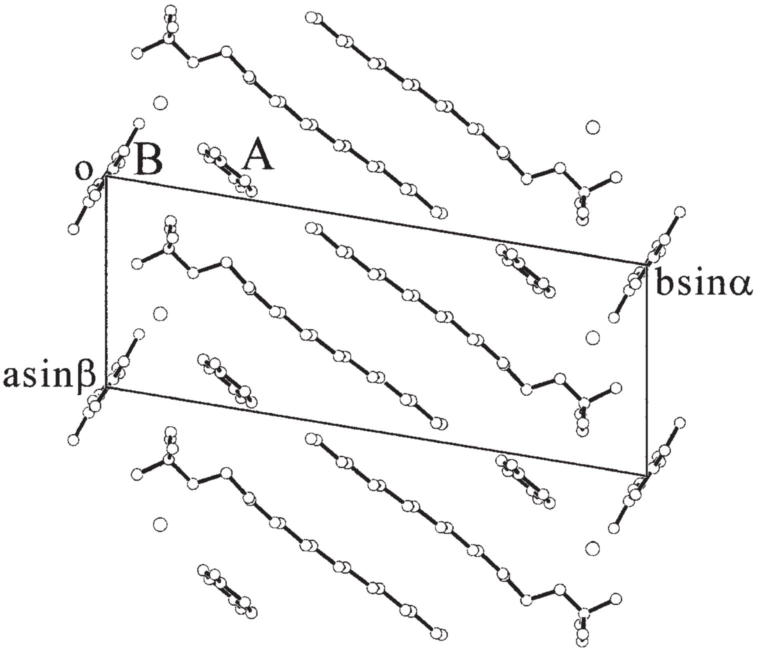

Fig. 5. Crystal structure of CDEAB/HQ viewed along the *c* axis.

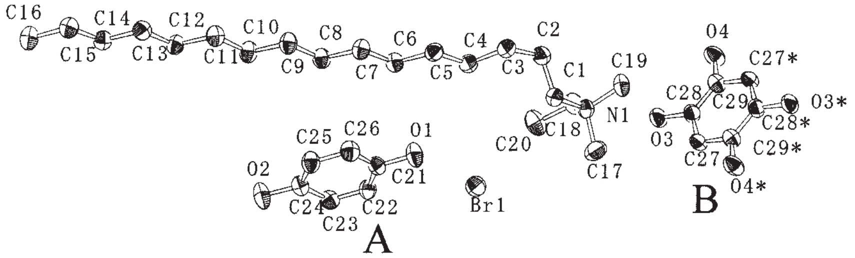

Fig. 6. Molecular structure of CDEAB/HQ with the atomic numbering. The thermal ellipsoids are shown with 50% probability.

one CDEAB and one and a half HQ molecules (A- and B-HQ, respectively) in an asymmetric unit. The A-HQ molecule is situated in the common packing pattern. The two OH groups of the A-HQ molecule make hydrogen bonds with the OH groups of the neighboring A-HQ molecules and the Br anions; the distances of the hydrogen bonds are 2.709(5) Å (O2···O1) and 3.221(4) Å (O1···Brl). The B-HQ molecule occupies an inversion center and takes a disordered structure. The two OH groups of the disordered HQ molecule make hydrogen bonds with the OH groups of the neighboring B-HQ molecules and the Br anions to form a linear chain along the *c* axis. The distances of the hydrogen bonds are 2.458(3) Å (O3···O3′ at $-x+2$, $-y$, $-z+1$), 3.216(2) Å (O3···Br1′ at $x+1$, y, z), and 3.138(2) Å (O4···Br1′ at $x+1$, y, z), respectively. Since the hydrogen-bond distances of the two disordered molecules are not so different, the occupancy factor becomes 50:50. The hexadecyl group of CDEAB has an all-trans conformation. The bond distances and angles of CDEAB and HQ are not significantly different from the corresponding ones of the reported one.

Stabilization of the HQ Molecules. Although the two complexes have different crystal systems, the molecular arrangements are very similar to each other. The results of stabilization experiments to light or air exposure are shown in Figs. 7 and 8, respectively, in which only the surfactant complexes with chloride anions are given. Although the crystal structures of the MDBAC/HQ, STAC/HQ, CTAC/HQ, and MTAC/HQ have not yet been determined, the complex formation was estimated from the UV spectra and powder X-ray diffraction. The HQ molecules in the surfactant complexes with chloride anions are clearly more stable than HQ alone. Similar results for surfactant complexes with bromide anions have already been reported.[6] The stabilization should be caused by the complex formation of HQ with the surfactant molecules.

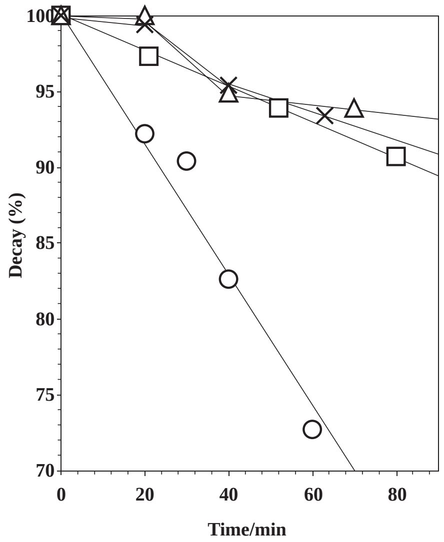

Fig. 7. Decay curves of HQ on exposure to the xenon lamp at 25 °C. The curves show HQ alone (○), benzyl(hexadecyl)dimethylammonium chloride (CDBAC)/HQ (□), benzyldimethyltetradecylammonium chloride (MDBAC)/HQ (△), hexadecyltrimethylammonium chloride (CTAC)/HQ (×), respectively.

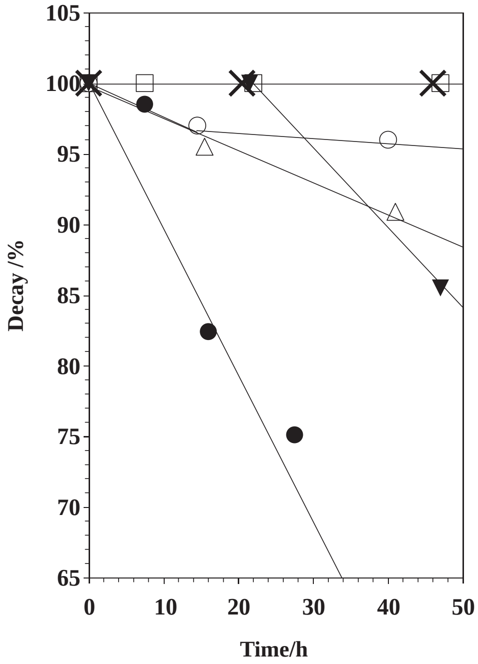

Fig. 8. Decay curves of HQ with time on exposure to oxygen gas at 37 °C. The curves show HQ alone (●), trimethyloctadecylammonium chloride (STAC)/HQ (□), benzyl(hexadecyl)dimethylammonium chloride (CDBAC)/HQ (×), trimethyltetradecylammonium chloride (MTAC)/HQ (○), hexadecyltrimethylammonium chloride (CTAC)/HQ (△), benzyldimethyltetradecylammonium chloride (MDBAC)/HQ (▼), respectively.

The HQ molecule forming the crystalline complexes with the CDBAC and CDEAB surfactants makes fairly strong hydrogen bonds with themselves and the anions. However, if the intermolecular interaction is only such hydrogen bonds, the complex may be easily soluble in an aqueous solution, and may be moisture-sensitive. As shown in Fig. 1 or Fig. 5, one of the HQ molecules is sandwiched with the alkyl groups from both sides of the benzene ring in the common packing pattern. The sandwiched structure, composed of fairly strong C–H···π hydrogen bonds, stabilizes the A-HQ molecules in complex formation. The B-HQ molecule is also sandwiched with the benzyl groups or ethyl groups of the neighboring surfactant molecules from both sides of the benzene ring, although the interatomic distances are somewhat longer than those of A-HQ. The distances of the typical C–H···π contacts of the A-HQ molecules are shown in Fig. 9. Not only the O–H···O and O–H···halogen hydrogen bonds, but also the C–H···π hydrogen bonds, make the HQ molecule covered with the surfactant molecules, and the crystalline complex becomes very stable to the external reagent and light. The above results suggest that if we select more suitable surfactants with longer alkyl chains, it may be possible to design more thermally stable complexes. Further experiments are in progress.

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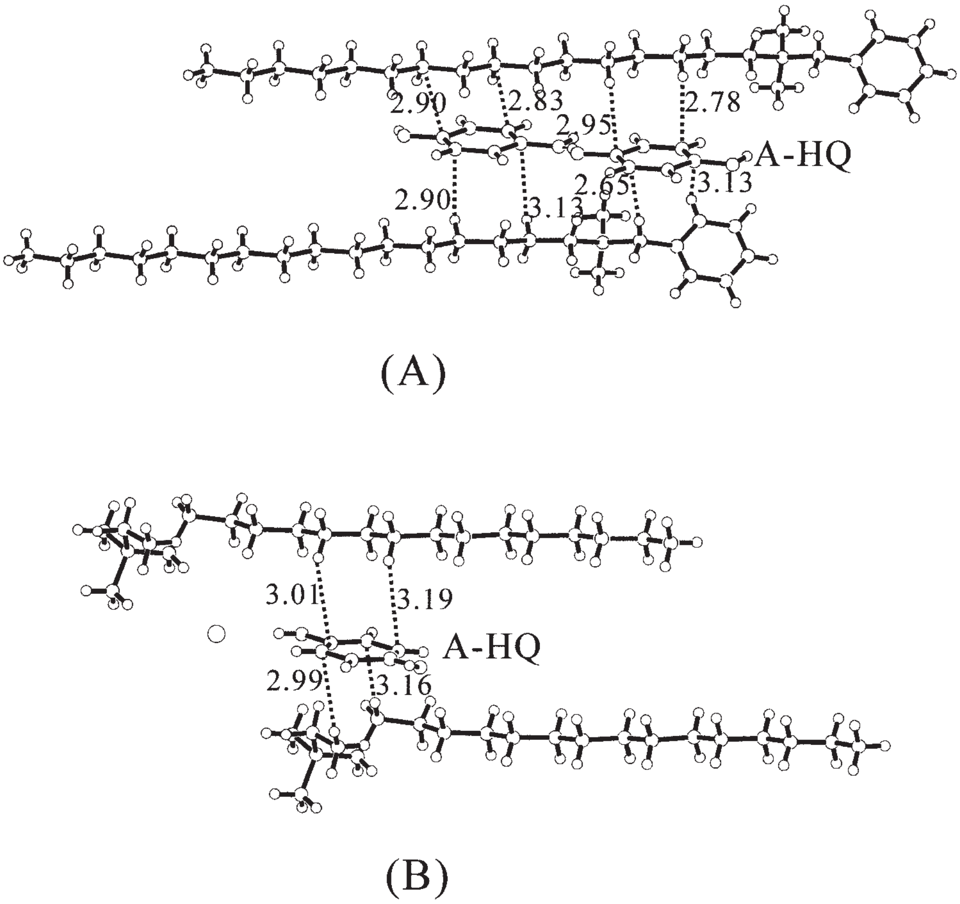

Fig. 9. The distances of the typical CH···π interactions in the CDBAC/HQ complex (A) and the CDEAB/HQ complex (B).

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