Remarkable selectivity of per-O-methylated tricationic $6^A,6^C,6^E$-tripyridinio-$6^A,6^C,6^E$-trideoxy-α-cyclodextrin for basic anions over non-basic anions

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Received (in Cambridge, UK) 30th January 2001, Accepted 8th June 2001
First published as an Advance Article on the web 12th July 2001

The per-O-methylated tricationic $6^A,6^C,6^E$-tripyridinio-$6^A,6^C,6^E$-trideoxy-α-cyclodextrin shows a high affinity for basic anions, especially highly charged phosphate and pyrophosphate anions, at near-neutral pH with association constants of 7 000 and 9 000 M^{-1}, respectively, but it did not bind non-basic anions, such as I^-, ClO_4^-, SCN^- or even doubly charged SO_4^{2-}, in contrast to the non-methylated counterpart. ^1H NMR spectral studies verify a plausible structure, in which the bound anion is located more closely to the pyridinio *meta* and *para* positions rather than to the *ortho* positions, due probably to the greater MeO- *vs.* HO-group hydrophobicity, which rejects deep intrusion of the anion into the positive cavity. Molecular mechanics calculations supported the above conclusions.

Crown ethers and cryptands have been developed as neutral organic receptors for cations, and have paved the way to advances in supramolecular chemistry;[1] thus, most of the early work in this field directed our attention to the exploitation of selective receptors for cations and neutrals.[2] On the other hand, designing neutral anion-binding molecules[3] potentially utilizable as anion-sensing devices specific for target ions such as biologically important phosphate[4] and sulfate ions[5] has recently attracted considerable attention. Meanwhile, quite recently, Matsui *et. al.* have prepared a series of anion-receptive cyclodextrin (CyD)-based pyridinium salts, *i.e.*, 6^A-mono-, $6^A,6^B$-di-, $6^A,6^C$-di-, $6^A,6^D$-di-, and $6^A,6^C,6^E$-tripyridinio-substituted α- or β- cyclodextrins[6] and have examined spectroscopically their anion-binding behaviour in aqueous solution; the association constants (K, M^{-1}) increase with increasing radii of inorganic ions; for example, Br^- (31.9) < NO_3^- (70.2) < I^- (1330) < SCN^- (3010) < ClO_4^- (6900) for the cationic $6^A,6^D$-dipyridinio-substituted α-CyD. Furthermore, $6^A,6^C,6^E$-tripyridinio-$6^A,6^C,6^E$-trideoxy-α-CyD (hereafter, ACE-α-CyD, Fig. 1a) has an association constant of 11 000 M^{-1} for I^-. Matsui has stated that electrostatic interactions as well as van der Waals attractions may add stability to the complex. Incidentally, this selectivity order is also in accord with the descending order of dehydration energies of the anions in the Hofmeister series. We report here on the effect of per-O-methylation of all the hydroxy groups of ACE-α-CyD, giving $6^A,6^C,6^E$-tripyridinio-$2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^B,6^D,6^F$-pentadeca-*O*-methyl-$6^A,6^C,6^E$-trideoxy-α-cyclodextrin (TPM-α-CyD, Fig. 1b), upon its complexation with various types of inorganic anion. The α-CyD framework seemed most suitable for this purpose, because the suspended pyridinio and the methoxy groups in the cationic host molecule are rigidly held in a *cis* position to each other in a C_3-symmetry on the narrower rim of the CyD. Prior to commencement of our study we had been inferring from CPK space-filling molecular models that per-O-methylation would comparatively destabilize such complexation as mentioned above, because the methyl-group substitution would sterically prohibit the pyridinio moieties from facing the included anion, thereby diminishing the contribution of such charge–charge and van der Waals tight contact between the included anion and the pyridinio moieties to the stability, and/or furthermore because the methyl substitution enhances the hydrophobicity of the inner wall of the positive region, which would disfavour the invasion of a hydrophilic species into it. Hence, the per-O-methylated TPM-α-CyD would be expected to exhibit an anion selectivity entirely distinct from that of the non-methylated ACE-α-CyD itself.

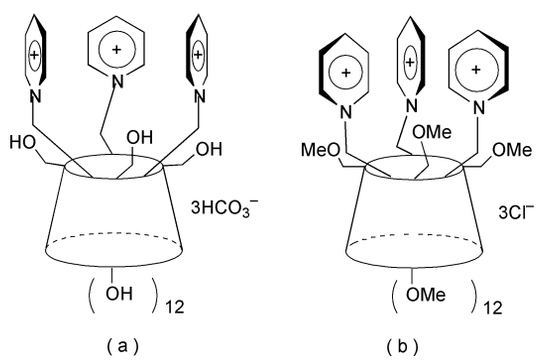

Fig. 1 Chemical structures of (a) ACE-α-CyD as HCO_3^- salt and (b) TPM-α-CyD as Cl^- salt.

Experimental

Materials

Pyridine was refluxed over CaH_2 and then distilled. The inorganic sodium salts (special grade), all commercially available from Wako Pure Chemicals or Tokyo Kasei Co. (Japan), were used as received. Solvents were reagent grade or better and were dried by following standard procedures.[7]

TPM-α-CyD was synthesized from the corresponding $6^A,6^C,6^E$-tris-*O*-methylsulfonyl-α-CyD according to a literature procedure[8] with a minor modification: the methanesulfonylated α-CyD (200 mg, 0.14 mmol) was dissolved in 10 mL of dry pyridine. The reaction mixture was heated at 70 °C for 8 h. Rotary-evaporation of the solvent, acidification with aq. 2% HCl, and purification by gel-column chromatography using Sephadex LH-20 gave the sulfonate salt of the desired final product. Conversion of the counter-anion ($MeSO_3^-$) to Cl^- through an anion-exchange column afforded TPM-α-CyD as a white powder exhibiting deliquescence (206 mg, 99%); mp

DOI: 10.1039/b101042p

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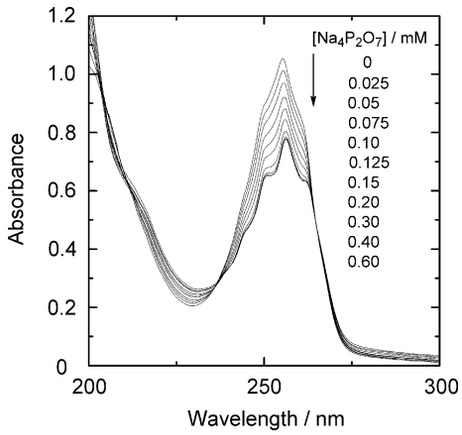

Fig. 2 UV titrations for TPM-α-CyD (5.0×10^{-5} mol dm^{-3}) with $Na_4P_2O_7$ at pH 8.0, 25 °C. The medium pH was adjusted to 8.0 with NaOH in individual measurements.

123–124 °C (decomp.); ^{1}H NMR of the pyridinium protons (D_2O; 400 MHz); δ 7.94 (t, 6H, *p*-H), 8.48 (t, 3H, m-H), 8.64 (t, 6H, *o*-H); IR (KBr; cm^{-1}) ν_{max} 1175.5 and 1353.9 cm^{-1} due to the sulfonate group lost; FAB-MS (pos.) *m*/*z*: Calc. for $C_{66}H_{102}Cl_2N_3O_{27}$: $[M - Cl^-]^+$, 1438.6. Found: *m*/*z*, 1438.6; $C_{61}H_{97}Cl_2N_2O_{27}$: $[M - Cl^- - py]^+$, 1359.6. Found: *m*/*z*, 1359.5; $C_{56}H_{92}Cl_2NO_{27}$: $[M - Cl^- - 2py]^+$, 1280.5. Found: *m*/*z*, 1280.5. The product was judged pure enough for spectroscopic measurements. Therefore, no further purification was attempted.

Spectroscopic measurements

A stock solution (10 mM) of TPM-α-CyD was prepared in distilled water containing 1 M NaCl to keep the ionic strength constant with a desired pH-value adjusted with aq. HCl or NaOH. Aliquots (10 μL) of the stock TPM-α-CyD solution adjusted to the same pH were placed in a UV cell. The final TPM-α-CyD concentration was 0.05 mM. To this solution was added an appropriate volume of an inorganic salt stock solution through a microsyringe, and the solution was mixed at 25 °C to establish an equilibrium quickly. Electronic absorption (UV) spectra were run on a Hitachi 220A spectrometer. UV spectral changes with increasing concentrations of, for instance, sodium pyrophosphate ($Na_4P_2O_7$) are represented in Fig. 2, where the change in ionic strength did not affect the UV absorbance at all. ΔA_{255} is the absorbance change at 255 nm before guest addition minus the absorbance at 255 nm after guest addition. Anion-binding titrations were performed by monitoring the UV absorbance at 255 nm as a function of added anion concentration. Double-reciprocal plots of ΔA_{255} against anion concentrations (C_a) afforded binding constants (K) from equation (1), where C_t is the total concentration of

$$1/\Delta A_{255} = 1/C_t K \Delta\varepsilon_{255} C_a + 1/C_t \Delta\varepsilon_{255} \quad (1)$$

TPM-α-CyD, and $\Delta\varepsilon$ is the change in extinction coefficient between the bound and unbound TPM-α-CyD.[9]

^{1}H NMR spectra were measured using a Nihondensi Detum α-400 spectrometer operating at 400 MHz. Chemical shifts (δ) are given in ppm and referenced to residual H_2O for measurements in water and to tetramethylsilane for measurements in acetonitrile-d_3. FAB-MS spectra were recorded on a Nihon Bunko JMS-7000T spectrometer.

CAMD calculations

Molecular mechanics/molecular dynamics calculations of the stabilization energies of the systems for model complexes between TPM-α-CyD or ACE-α-CyD and HPO_4^{2-} were performed with CHARMm Ver 22/QUANTA Ver 3.3 (Molecular Simulation Inc., San Diego, CA) on Indigo R-4000 (Silicon Graphics Corp., Mountain View, CA) hardware. The intermolecular interaction energies (ΔE; kJ mol^{-1}) have been calculated as the difference between the energy of the complex and the sum of the energies of the separated molecules.

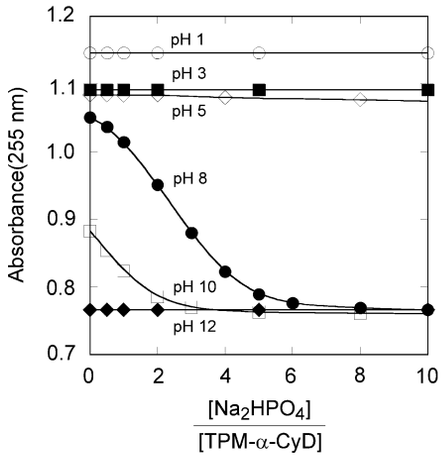

Fig. 3 Plots of the 255 nm absorbance *vs.* $[Na_2HPO_4]$/[TPM-α-CyD] ratios at various pHs. [TPM-α-CyD] = 5.0×10^{-5} mol dm^{-3}.

Results and discussion

An aqueous solution (pH 8.0) of TPM-α-CyD afforded a UV spectrum involving a maximum absorption at 255.5 nm ($\varepsilon = 7100$ M^{-1} cm^{-1}/Py$^+$) due to the pyridinium moiety, as shown in Fig. 2. The fact that the reference compound 1-ethylpyridinium bromide had a larger molar absorptivity in less polar methanol (258.6 nm, $\varepsilon = 7220$ M^{-1} cm^{-1}) than in water (258.3 nm, $\varepsilon = 4180$ M^{-1} cm^{-1}) obviously supports the notion that the pyridinio moiety in TPM-α-CyD experiences a more hydrophobic microenvironment attributable to the attached CyD framework. Fig. 3 shows plots of the altering absorbances at 255 nm as a function of concentration of Na_2HPO_4 ($pK_{a1} = 2$, $pK_{a2} = 7$, $pK_{a3} = 12$) at various solution pHs. Fig. 3 shows that the addition of Na_2HPO_4 to a TPM-α-CyD solution at pH ≤ 5 exerted no influence on the absorption. This observation demonstrates that the complexation with dihydrogen phosphate monoanion ($H_2PO_4^-$) is unfavourable due to the lack of sufficient basicity and/or negative charge, although the monoanion is the predominant species in the pH 2–5 region.

However, a significant decrease in the UV absorbance took place with increasing concentrations of Na_2HPO_4 at a constant pH of 8, suggesting that anion-binding to TPM-α-CyD enhances the polarity of the surroundings around the pyridinio moieties to result in the reduction in UV absorbance. Furthermore, the spectral change is indicative of TPM-α-CyD complexation with either of HPO_4^{2-} or PO_4^{3-}. There can be no possibility of the participation of PO_4^{3-}, because phosphate anions at pH 8 exist predominantly as a mixture of $H_2PO_4^-$ (minor) and HPO_4^{2-} (major) rather than PO_4^{3-}. If HPO_4^{2-} lost its remaining proton upon its invasion into the positive area, the phosphate ion should be bound to TPM-α-CyD in the triply anionic form; namely, there might be a possibility that the included HPO_4^{2-} ion undergoes immediate deprotonation by complexation. Nevertheless, this inference is not the case, because both phenyl phosphate (Ph-OPO_3^{2-}) and β-D-glucose 6-phosphate are capable of undergoing complexation to almost the same extent as HPO_4^{2-} itself under identical conditions. Hence, we can conclude that HPO_4^{2-} alone participates in the complexation event at such a near-neutral pH.

As depicted by the bold line in Fig. 4, the UV absorbance decreases with increasing pH-value in the region pH > 10 even in the absence of the salt, and reaches a constant value at

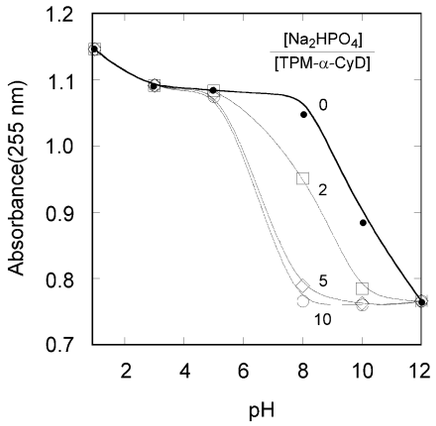

Fig. 4 Plots of the 255 nm absorbance *vs.* pHs at various $[Na_2HPO_4]$/[TPM-α-CyD] ratios in water. [TPM-α-CyD] = 5.0×10^{-5} mol dm^{-3}. The lines are arbitralily drawn. The data were taken from Fig. 3.

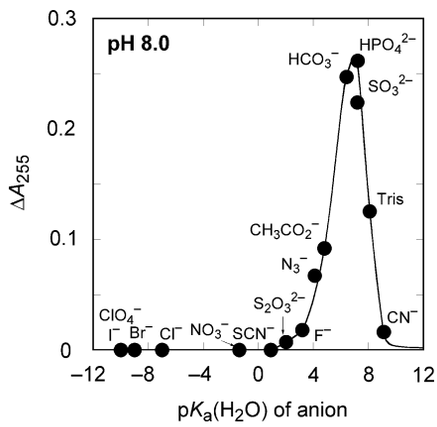

Fig. 5 Plots of the changes in ΔA_{255} at pH 8.0 *vs.* the pK_a values of various anions (2.5×10^{-4} mol dm^{-3}) in water.

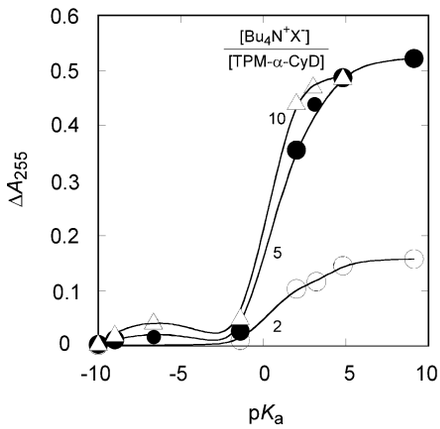

Fig. 6 Plots of the changes in ΔA_{255} *vs.* the pK_a values of various anions (X^-) in acetonitrile. [TPM-α-CyD] = 5.0×10^{-5} mol dm^{-3}. (a) $[Bu_4N^+X^-] = 1.0 \times 10^{-4}$ mol dm^{-3} (○), (b) $[Bu_4N^+X^-] = 2.5 \times 10^{-4}$ mol dm^{-3} (●), (c) $[Bu_4N^+X^-] = 5.0 \times 10^{-4}$ mol dm^{-3} (Δ).

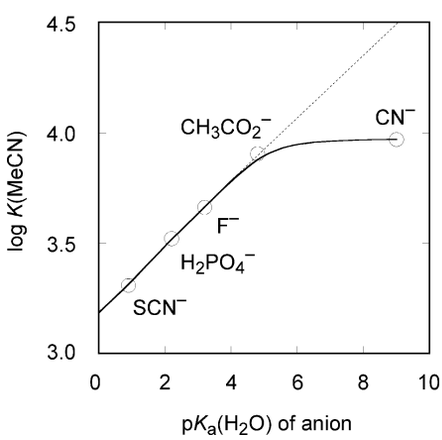

Fig. 7 A plot of log K(MeCN) *vs.* pK_a(H_2O).

pH 12. In particular, the addition of the salt at pH 12 has absolutely no effect on the absorbance (Fig. 3), implying that OH^- ion is the only species attributable to the decreased absorbance at pH 12. Therefore, the UV measurements described below were performed at pH 8, unless otherwise noted.

As shown in Fig. 5, no changes in the UV spectra were found with I^-, ClO_4^-, Br^-, or SCN^- monoanions, or even SO_4^{2-} dianion, all these ions commonly possessing a pK_a-value less than 1, indicating that TPM-α-CyD generally failed to bind any non-basic anions arising from strong acids. However, a decrease in the UV absorption took place when a number of basic anions, such as not only a monoanion like CH_3CO^{2-}, but also dianions like $S_2O_3^{2-}$, CO_3^{2-}, HPO_4^{2-} and SO_3^{2-} were added. Thus, it is obvious that the strength of the anion binding strongly depends on the basicity of the anionic species of the added salts rather than their ionic radii; namely, the higher the basity, the stronger the binding to TPM-α-CyD of the anion having a pK_a-value less than 7; of the tested anionic bases the highly charged $P_2O_7^{4-}$ ion has the highest binding ability (data not shown here).

The very same situation emerged for anion complexation using the tetrabutylammonium salts in acetonitrile, a typical aprotic solvent; as Fig. 6 shows, the higher the basicity, the stronger the complexation. Fig. 7 displays a plot of the logarithmic association constants [log K(MeCN)] *vs.* the coresponding pK_a(H_2O)-values in water. These findings strongly indicate that the major driving force, *i.e.*, the mechanism for the complexation, must be essentially the same in both water and acetonitrile.

Furthermore, Fig. 5 shows that aqueous CN^- exhibits only an unexpectedly low complexation ability in spite of its having a higher binding potency (pK_a = 9.0), perhaps because the anionic species required for binding exists in only a fairly low equilibrium concentration at pH 8. In fact, Fig. 6 reveals that the inherent high binding ability of CN^- can be considerably restored with the naked anion CN^-, which was added as the tetrabutylammonium salt in acetonitrile. Meanwhile, the low binding affinity of aqueous tris(2-hydroxyethyl)methylamine (Tris) can be interpreted similarly; namely, TPM-α-CyD appears to bind only the anionic form, $H_2NC(CH_2CH_2OH)_n(CH_2CH_2O^-)_{3-n}$, being present in small quantities, which is in equilibrium with neutral $H_2NC(CH_2CH_2OH)_3$, cationic $H_3N^+C(CH_2CH_2OH)_3$, and betaine $H_3N^+C(CH_2CH_2OH)_n(CH_2CH_2O^-)_{n-3}$ forms.

In general, ^{1}H NMR spectra will allow the ambiguous positioning of the basic anion in the host molecule. Table 1 shows the ^{1}H NMR chemical shifts of the *ortho*-, *meta*-, and *para*-protons in the pyridinio moiety in the absence and presence of the phosphate salt at pH 3–11. The effects of changing phosphate concentrations on the absorbance were strongly pH-dependent; at pH 4 all the signals were unaltered; at pH 7, however, the signal due to the *para*-protons showed the largest upfield shift, in particular, in the presence of high salt concentrations; the *meta*-protons showed the second largest, and the *ortho*-protons the least.

Table 1 also demonstrates that, although a solution pH as high as 11 rendered the chemical shift of the pyridino protons considerably upfield, the addition of Na_2HPO_4 to the TPM-α-CyD solution at the same pH did not affect the NMR spectra; hence, the large ^{1}H NMR upfield shift in the absence of salts

Table 1 Effects of added phosphates on the ^{1}H NMR chemical shifts of the pyridinio protons in TPM-α-CyD at various pD's[a]

Phosphate	mM	pD	*ortho*	*meta*	*para*
NaH_2PO_4	0	3.0[b]	8.75 (0)	8.05(0)	8.60(0)
NaH_2PO_4	100	4.0	8.74 (+0.01)	8.04 (+0.01)	8.58 (+0.02)
Na_2HPO_4	0	7.0[b]	8.60 (+0.15)	7.70 (+0.35)	8.16 (+0.44)
Na_2HPO_4	100	7.0[b]	8.51 (+0.24)	7.47 (+0.58)	7.90 (+0.70)
Na_2HPO_4	0	11.0[c]	8.48 (+0.27)	7.42 (+0.63)	7.84 (+0.76)
Na_2HPO_4	100	11.0[c]	8.48 (+0.27)	7.41 (+0.64)	7.84 (+0.76)

[a] Conditions: [TPM-α-CyD] = 5.0 mM; 25 °C; ionic strength 1.0 (NaCl). The plus signs in parentheses denote an upfield shift from the chemical shift at pD 3.0. [b] The pD was adjusted with aq. HCl. [c] The pD was adjusted with aq. NaOH.

Table 2 Additive effects of various anions on the ^{1}H NMR chemical shifts of the pyridinio hydrogens in TPM-α-CyD in CD_3CN[a]

Anion	mM	*ortho*	*meta*	*para*
—	—	8.74 0)	8.01(0)	8.53(0)
I−	25	8.74 (0)	8.01 (0)	8.54 (−0.01)
I−	50	8.75 (−0.01)	8.02 (−0.01)	8.55 (−0.02)
Cl−	50	8.73 (+0.01)	7.99 (+0.02)	8.52 (+0.01)
H_2PO_4−	25	8.65 (+0.09)	7.66 (+0.35)	8.12 (+0.41)
CH_3CO_2−	25	8.58 (+0.16)	7.40 (+0.61)	7.81 (+0.72)
CN−	10	8.65 (+0.09)	7.65 (+0.36)	8.11 (+0.42)
CN−	25	8.57 (+0.17)	7.33 (+0.66)	7.74 (+0.83)
CN−	50	8.55 (+0.19)	7.33 (+0.66)	7.74 (+0.83)

[a] Conditions: [TPM-α-CyD] = 5.0 mM; 25 °C. The plus and minus signs in parentheses denote upfields and downfield shifts, respectively from the chemical shifts without a tetrabutylammonium salt.

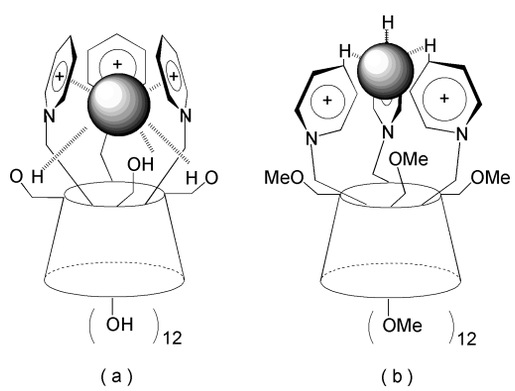

Fig. 8 (a) The postulated structure for the ACE-α-CyD/anion complex and (b) the most reasonable structure for the TPM-α-CyD/anion complex.

is primarily indicative of the interaction of the TPM-α-CyD pyridinum moiety with OH^- ion, supporting the suggestion obtained from the UV experiment. Of course, no change in the UV and NMR spectral pattern was revealed with 1-ethylpyridinium bromide under the same circumstances.

Table 2 shows also comparatively greater upfield shifts of the *para* and *meta vs. ortho* protons, which were induced by addition of several basic anions in acetonitrile, reconfirming that the anionic species interact preferentially with the *para*- and *meta*-protons irrespective of the solvents employed. The observed large affinity of TPM-α-CyD for basic anions might be attributed to the hydrogen-bond-like interactions of the *meta* and *para* protons with the complexed anion;[10] namely, the anionic guest is complexed by virtue of its hydrogen bonds with the *meta* and *para* pyridinio protons complemented by the charge interaction. However, other subtle influences may govern the binding features as well. Actually, TPM-α-CyD did not give rise to a charge-transfer band with I^-, CN^- and SCN^-, but provided a weak charge-transfer band at 310 nm with CN^- alone. The putative structure of the complex consistent with the NMR data is illustrated in Fig. 8b. The symmetric structure

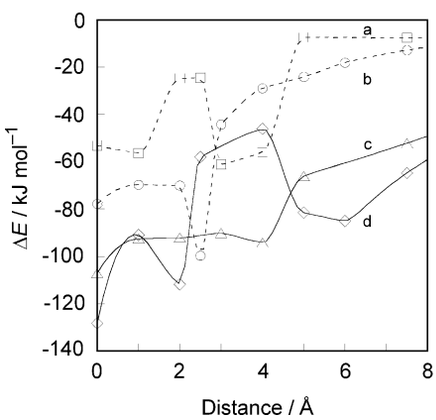

Fig. 9 Intermolecular interaction energies (ΔE/kJ mol^{-1}) for the complexations as a function of the intermolecular distance between the centers of the CyD's glucose unit and HPO_4^{2-}. (a) ACE-α-CyD/HPO_4^{2-}, (b) ACE-α-CyD/HPO_4^{2-}/H_2O, (c) TPM-α-CyD/HPO_4^{2-}, (d) TPM-α-CyD/HPO_4^{2-}/H_2O.

illustrated in Fig. 8b is rather speculative, but the unsymmetric structure may be really favoured. Further computational study is needed to settle the detailed structure.

These observations are in sharp contrast to the already reported case with the non-O-methylated 6^A-pyridinio-6^A-deoxy-α-CyD (A-α-CyD), exhibiting the largest downfield shift for the *ortho* protons;[6a] it was proposed there that lipophilic, non-basic anions such as I^-, ClO_4^- and SCN^- ($pK_a < 1$) are accommodated into the mostly positively charged region inside the A-α-CyD molecule, where both the hydrogen bonds with the CyD's hydroxy groups and the lower desolvation energies of these basic anions might permit their deep entry into the most positive region. Moreover, it may be the reason that the soft bases such as I^-, ClO_4^- and SCN^- like the soft acids with a diffused positive charge.[11] In full accord with the inference that aqueous I^-, CN^- and SCN^- are retained at the depth of the *ortho* positions on the π-face, they gave rise to the significant charge-transfer band at 310 nm. The plausible structure of this complex is illustrated in Fig. 8a.

In order to verify the above conclusions, molecular mechanics calculations followed by molecular dynamics calculations of total complexation energies (E, kJ mol^{-1}), were performed. The major question posed here is whether there is an energetic benefit to the structures depicted in Fig. 8a and 8b. Fig. 9 depicts plots of intermolecular interaction energies (ΔE) for the complexations as a function of the distance between the centers of the anion and the CyD's glucose moiety; the methylated TPM-α-CyD/HPO_4^{2-} complex (line c) is 30 kJ mol^{-1} below the non-methylated ACE-α-CyD/HPO_4^{2-} complex at 3 Å (lines c and a). However, there is no indication of distinct deep energy mimima at a distance of more than 3 Å in either case. On the other hand, the mere addition of only one water molecule to the HPO_4^{2-} ion results in the production of a fairly deep energy minimum at 6 Å for TPM-α-CyD (line d), and one of 2.5 Å for ACE-α-CyD (line b). This is

what we have expected, and strongly supports the conclusions made above.

In conclusion, it is quite dramatic that the anion selectivity of TPM-α-CyD totally differed from that of the corresponding non-O-methylated ACE-α-CyD; irrespective of the solvent property being protic or aprotic, the former host acted exclusively on basic anions, but the latter host acted rather on non-basic anions. Both the lack of any explicit hydrogen-bond-donation ability of the methoxy groups and the enhanced hydrophobicity around the binding region appear to be the most acceptable explanation for the altered anion selection.

Acknowledgements

We thank Dr M. Koide and Mr M. Hattori (Lion Corporation) for CAMD calculations.

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