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Dielectric behaviour of α-cyclodextrin, heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin, randomly methylated β-cyclodextrin and low frequency Raman spectra of α- and β-cyclodextrins

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The frequency and temperature dependence of the real (ε') and imaginary (ε'') parts of the dielectric constant of α-cyclodrextrin (form 1; α-CD·5.9H_2O) and α-cyclodextrin (form III; α-CD·7.6H_2O) and of the corresponding dried forms (α-CD·1.1H_2O, α-CD·2.9H_2O, respectively) has been investigated over the frequency range 0–100 kHz and temperature range 130–350 K. In addition the dielectric behaviour has been investigated of heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin (β-CD·TRIME·0.3H_2O) and randomly methylated β-cyclodextrin (β-CD·RAME·0.8H_2O). The dielectric behaviour is described well by Debye-type relaxation (α-disperson). All α-CD systems exhibit an additional Ω-dispersion at low frequencies, which is attributed to proton transport. The fact that the ε' values of α-CD form III are larger than those of α-CD form I is attributed to the different numbers and different strengths of the intramolecular hydrogen bonds. Form III has a stable conformation which is shown by the constant values of ε' in the temperature range 125–250 K. By contrast, in form I the ε' values increased linearly with temperature, indicating that the system passed through succesive conformations. The temperature dependence of ε'' and phase shift φ in all the specimens of α-CD (forms I, III) and fully methylated β-CD do not reveal any order–disorder transition, because the developed hydrogen bonds ae not of the flip-flop type according to their crystal structures. The partially methylated β-CD reveals the characteristics of the order–disorder transition, which was observed before in the systems dried β-CD·2H_2O and non-dried β-CD·9.8H_2O. There is a direct relation between the hydroxyl groups of β-CD and the order–disorder transition. The order–disorder transition could also be shown in dried β-CD·2.4H_2O and non-dried β-CD·9.8H_2O samples but not in dried α-CD·1.1H_2O and non-dried α-CD·5.9H_2O samples, by low frequency Raman spectroscopy ($<180\,\mathrm{cm}^{-1}$). The step-like temperature dependence of the band at 33.7 cm^{-1} reveals a transition at about 223 K for both β-CD samples. In the case of α-CD samples the almost linear temperature dependence of the band at 49.1 cm^{-1} does not reveal any transition.

1. Introduction

It has been shown [1] that the dielectric behaviour of β-cyclodextrin (β-CD·9.8H_2O), its complex with 4-t-butylbenzyl alcohol (β-CD·TERB·11.2H_2O) and their dried forms, β-CD·2.4H_2O and β-CD·TERB·3.8H_2O, respectively, is described well by a Debye-type relaxation (α-dispersion). All systems except (β-CD·TERB·3.8H_2O) exhibited an additional Ω-dispersion at low frequencies. A transition temperature was indicated by a peak of the imaginary part of the dielectric constant ε'' and as a minimum of the phase shift component φ of the current passing through the sample relative to the applied signal. The transition is due to the disordered hydroxyl β-CD groups and water molecules that change into an ordered sate or, according to Saenger *et al.* [2, 3], that the flip-flop-type hydrogen bonds are transformed into the normal type.

The smallest member, α-cyclodextrin has been studied by X-ray and neutron diffraction in three forms: α-CD·6H_2O (I [4, 5], II [6]) and α-CD·7.57H_2O (III [7]). In α-CD forms I and II, all water molecules are well ordered and only the hydroxyl O(6)1 of glycose 1 is twofold disordered with occupancies 92% and 8%. In form I two water molecules are located inside the cavity. In form II only one water molecule and the primary O(6) hydroxyl of an adjacent α-CD molecule are in the centre of the cavity with five of the remaining water molecules located outside. In form III 2.57 water molecules are enclosed within the cavity and distributed over four

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sites of approximately 0.64 occupancy each. The remaining 5 water molecules are outside the cavity. In these crystal structures of α-CD no flip-flop type hydrogen bonds were observed, as in the case of β-CD [1]. Therefore it is expected that the α-CD systems do not exhibit an order–disorder transition as in the β-CD.

In the present work we investigate the dielectric properties of polycrystalline specimens, dried α-CD·$1.1H_2O$ and non-dried α-CD·$5.9H_2O$ of form I, dried α-CD·$2.9H_2O$ and non-dried α-CD·$7.6H_2O$ of form III over the frequency range 0–100 kHz and temperature range 120–300 K. In addition we confirm the above mentioned crystallographic results [4–7] of α-CD in two ways: (a) by dielectric spectroscopy and (b) by Raman spectroscopy. Neither method reveals a transition temperature in any form of α-CD, in contrast to β-CD, for which both methods reveal an order–disorder transition. Moreover, we investigate the dielectric behaviour of heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin (β-CD·TRIME·$0.3H_2O$), in which all the hydroxyl groups of β-CD are methylated, and of randomly methylated β-cyclodextrin (β-CD·RAME·$0.8H_2O$), in which some OH groups of β-CD are not methylated, in order to make sure that the order–disorder transition is connected with the hydroxyl groups in β-CD and the intramolecular hydrogen bonds $O(2)\cdots O(3')$ between adjacent glucose units.

2. Experimental

α-Cyclodextrin and randomly methylated β-cyclodextrin were purchased from Fluka Chemika, heptakis-(2,3,6-tri- *O*-methyl)-β-cyclodextrin was purchased from Cyclolab. The α-cyclodextrin was recrystallized (non-dried sample) once from water and then it was dried in the air for 5 minutes. A second sample (dried sample) was dried in an oven kept at 45 °C for 2 days and then it was kept in a desiccator. α-Cyclodextrin form III was obtained while crystallizing α-CD from 1.2 M $BaCl_2$ solution according to [7]. Thermogravimetric analysis (TA Instruments 2050, heating rate 10 °C min^{-1}) was used to determine the water content. The water content of the non-dried and dried α-CD form I was determined to be 5.9 and 1.1 water molecules, respectively, i.e. α-CD·$5.9H_2O$ and α-CD·$1.1H_2O$. From X-ray diffraction measurements the unit cell constants of both α-CD·$5.9H_2O$ and α-CD·$1.1H_2O$ are found to be almost the same as those of type I found by Klar *et al.* [5]. The geometrical characteristics of form I are prismatic crystals, as in our case, instead of tubular and flaky crystals in form II. The water content of α-CD form III was determined to be 7.6 water molecules for the non-dried sample (α-CD·$7.6H_2O$) and 2.9 water molecules for the dried sample (α-CD·$2.9H_2O$). The water content of the β-CD·TRIME and β-CD·RAME was determined to be 0.3 and 0.8 water molecules, respectively (β-CD·TRIME·$0.3H_2O$ and β-CD·RAME· $0.8H_2O$). The experimental procedure for the dielectric measurements is described elsewhere [1].

Raman scattering at 90° to the incident beam was recorded by means of a Spex Ramalog spectrometer fitted with a 1403 double monochromator, and with a third (1442U) monochromator operated in scanning mode. The light source was a Coherent Innova 90 argon-ion laser operated at 514.5 nm and 200 mW. Operating conditions were as follows: bandwidth 0.5 cm^{-1}, scanning increment 0.05 cm^{-1}, integration time 6 s. The low frequency scale was calibrated by reference to the 9.6 cm^{-1} and 14.9 cm^{-1} bands in the low frequency spectrum of L-cystine. Samples were enclosed in capillary tubes and held at a constant temperature (± 1 K) in the range 150–293 K, by means of a Harney–Miller cell (available from Spex Industries Inc.). The intensity of a Raman band was observed over a period of time to ensure equilibrium of the sample at a given temperature.

3. Results

3.1. *Dielectric spectroscopy*

The temperature dependence of ε' and ε'' over the range 125–300 K is shown in figure 1 for the samples α-CD·$5.9H_2O$, α-CD·$1.1H_2O$, in figure 2 for the samples α-CD·$7.6H_2O$, α-CD·$2.9H_2O$ and in figure 3 for the samples β-CD·TRIME·$0.3H_2O$ and β-CD·RAME·$0.8H_2O$.

In α-CD form I the ε' values of dried α-CD·$1.1H_2O$ increase linearly with temperature from 2.86 to 4.74 (figure 1). The corresponding values of non-dried α-CD·$5.9H_2O$ are almost the same as those of α-CD·$1.1H_2O$ over the temperature range 125–200 K but at higher temperatures they increase rapidly. The same picture is observed for the other higher fixed frequencies. The ε'' values of α-CD·$1.1H_2O$ vary slightly with temperature (between 0.05 and 0.35) over the temperature range 125–300 K. In the case of α-CD·$5.9H_2O$ the ε'' values coincide with those of α-CD·$1.1H_2O$ for temperatures $T < 200$ K. For higher temperatures the ε'' values increase rapidly.

In α-CD form III the ε' values of non-dried α-CD·$7.6H_2O$ and dried α-CD·$2.9H_2O$ samples, at 200 Hz, are almost the same (5 units) over the temperature range 130 K–230 K, but at higher temperatures they increase exponentially and divert from each other (figure 2). The same behaviour is observed for ε''. For temperatures $T < 230$ K the ε'' values are almost constant and equal to 0.25 units, but at $T > 230$ K they increase exponentially with temperature.

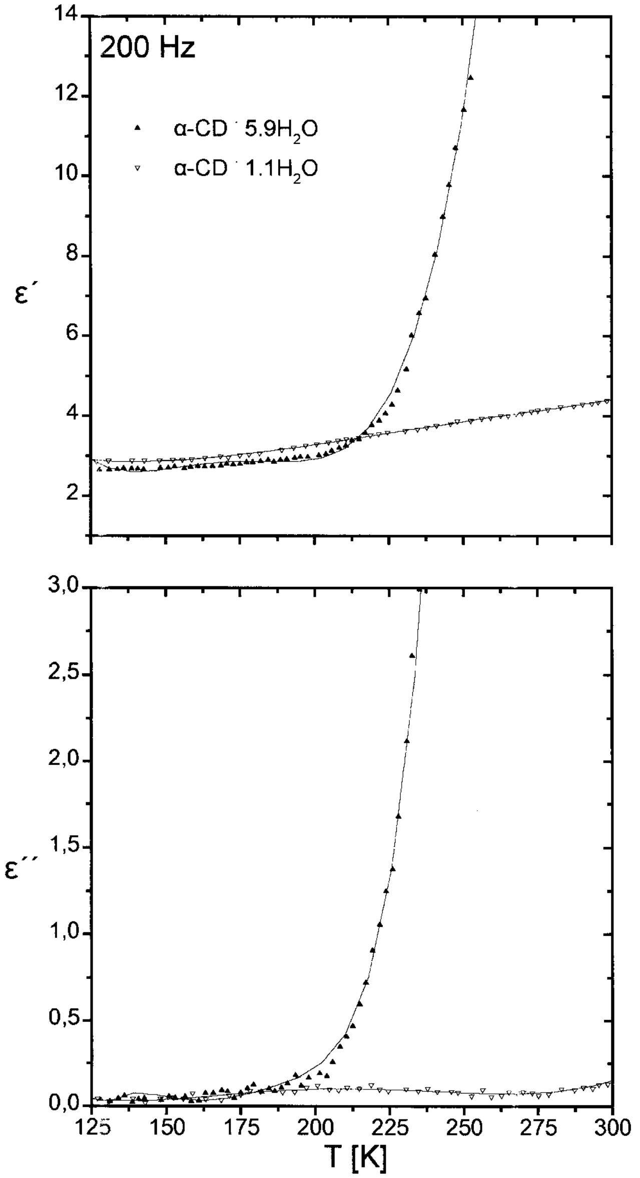

Figure 1. Temperature dependence of real (ε') and imaginary (ε'') parts of the dielectric constant of α-CD·1.1H$_2$O and α-CD·5.9H$_2$O at 200 Hz.

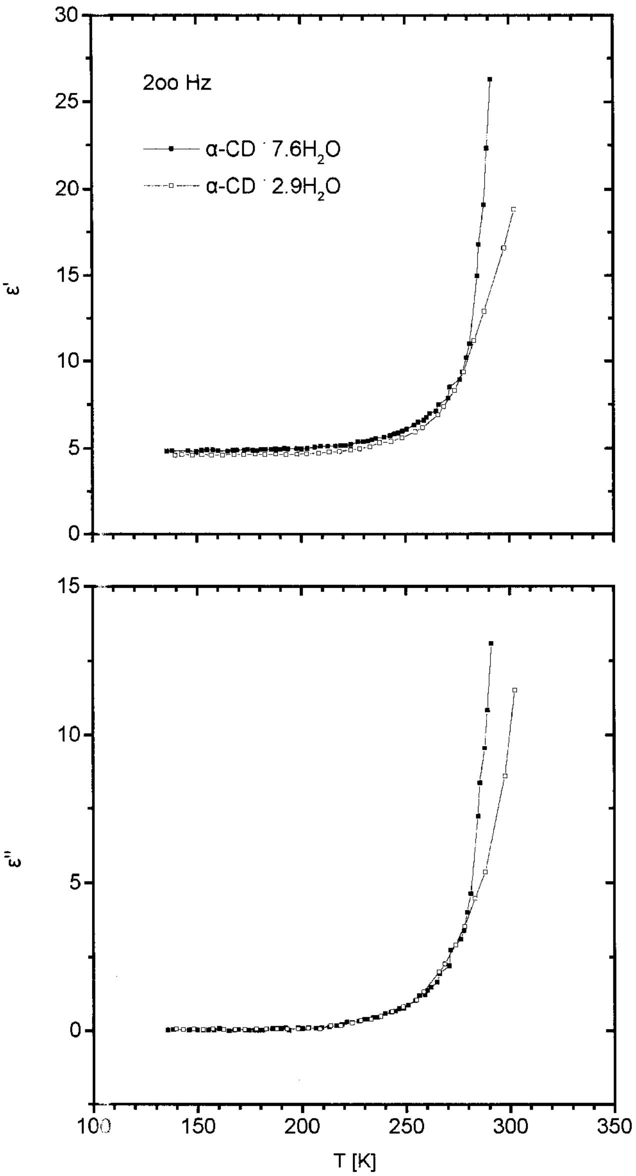

Figure 2. Temperature dependence of real (ε') and imaginary (ε'') parts of the dielectric constant of α-CD·2.9H$_2$O and α-CD·7.6H$_2$O at 200 Hz.

The ε' values of β-CD·RAME·0.8H$_2$O (figure 3) at a fixed frequency of 200 Hz increase with temperature in a step-like form from 2.55 to 3.78 ($\Delta\varepsilon' = 1.23$) over the range 125–300 K. The corresponding ε' values of β-CD·TRIME·0.3H$_2$O increase slightly from 2.49 to 2.82 ($\Delta\varepsilon' = 0.33$). The ε'' versus T curve of β-CD·RAME·0.8H$_2$O at 200 Hz is a broad bell shape with a maximum value of 0.21 at 200 K and a half-width of 75 K. The corresponding ε'' values of β-CD·TRIME·0.3H$_2$O vary between 0.01 and 0.08 and the curves do not exhibit any detectable bell-shape.

The ε' versus frequency curves have a sigmoid shape for every sample we examined, with the inflection point at around 20 kHz. The frequency variation of ε'' has the form of a dielectric loss peak, centred at a characteristic frequency $f_{\max}$. The ε' value is a measure of the polarization stored in the dielectric per cycle, while the ε'' value accounts for the part of the electrical energy that cannot be stored, but instead is thermally dissipated (loss). In the cases of β-CD·RAME·0.8H$_2$O and β-CD·TRIME·0.3H$_2$O only the α-dispersion is apparent. In the cases of α-CD·5.9H$_2$O, α-CD·1.1H$_2$O, α-CD·

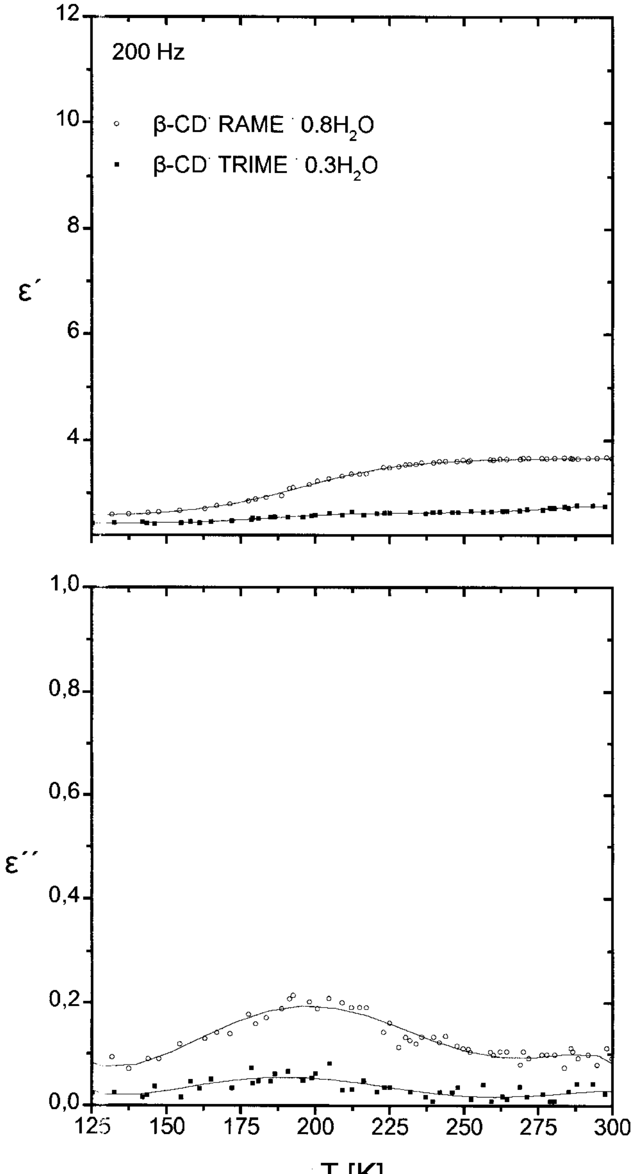

Figure 3. Temperature dependence of real (ε') and imaginary (ε'') parts of the dielectric constant of β-CD·TRIME·0.3H$_2$O and β-CD·RAME·0.8H$_2$O at 200 Hz.

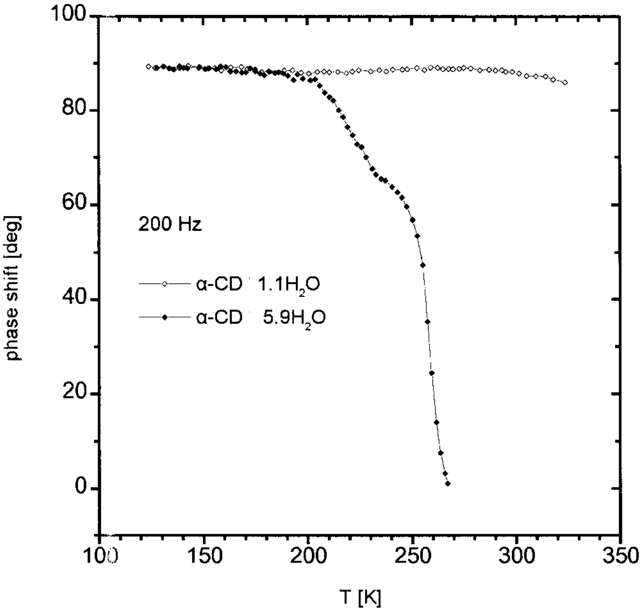

Figure 4. Temperature dependence of phase shift for dried sample α-CD·1.1H$_2$O (form I) and non-dried sample α-CD·5.9H$_2$O (form I) at 200 Hz.

7.6H$_2$O and α-CD·2.9H$_2$O both α- and Ω-dispersions are observed. The $\varepsilon''_{\max}$ values of each loss peak increase with temperature from 1.41 to 2.26 for α-CD·1.1H$_2$O, from 1.27 to 1.84 for β-CD·RAME·0.8H$_2$O and from 1.20 to 1.36 for β-CD·TRIME·0.3H$_2$O over the temperature range 130–330 K. In α-CD·5.9H$_2$O the $\varepsilon''_{\max}$ values increase continuously from 1.33 to very large values; then, at temperatures higher than 250 K, the bell shaped curve is destroyed. The Debye-type relaxation is no longer valid because the contribution of conductivity to ε'' is significant and gives rise to the large Ω-dispersion ([1], equation (5)). Finally, in both α-CD·7.6H$_2$O and α-CD·2.9H$_2$O the $\varepsilon''_{\max}$ values increase from 2.38 to 5.72 over the temperature range 130–330 K, and the curves keep their bell shape at all the temperatures studied.

The phase shift of α-CD·1.1H$_2$O, at a fixed frequency of 200 Hz (figure 4) over the temperature range 125–275 K has a constant value of 89°. Constant values 86°, 62°, 22° and 12° of phase shift are obtained, respectively, for other fixed frequencies of 1 kHz, 10 kHz, 50 kHz, 100 kHz. The same values as those of α-CD·1.1H$_2$O are obtained also for the samples of α-CD·5.9H$_2$O, α-CD·7.6H$_2$O and α-CD·2.9H$_2$O (figures 4 and 5) over the temperature range $T < 200$ K, but for temperatures $T > 200$ K they decrease rapidly. Constant values of phase shift are obtained also for the temperature dependence of fully methylated β-CD (β-CD·TRIME·0.3H$_2$O) (figure 6). In the case of partially methylated β-CD (β-CD·RAME·0.8H$_2$O) the temperature dependence of the phase shift presents a minimum at a temperature of 200 K (figure 6). At 200 Hz the phase shift of β-CD·RAME·0.8H$_2$O drops from 88° to 86° at 200 K and then increases again to 88°. For the other fixed frequencies the phase shift varies in a similar way.

3.2. *Low frequency Raman spectroscopy* (< *180 cm^{-1}*)

Figure 7 shows representative low frequency Raman spectra of β-CD·2.4H$_2$O at different temperatures. The temperature dependence of the 33.7 cm^{-1} band at 293 K

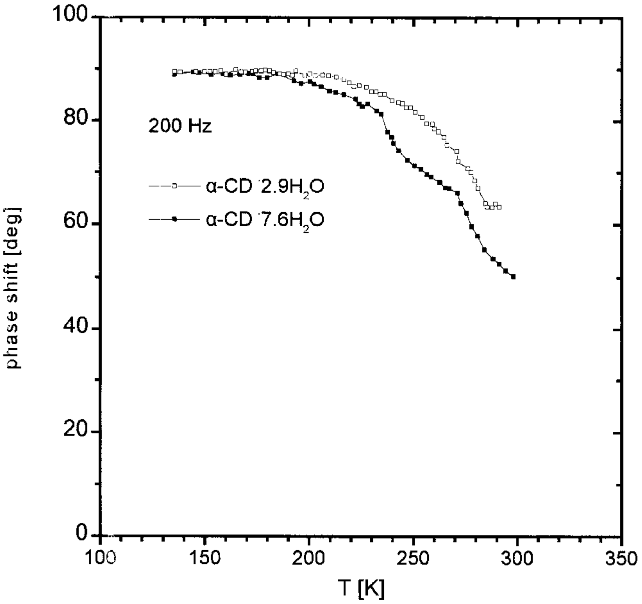

Figure 5. Temperature dependence of phase shift for dried sample α-CD$\cdot$2.9H_2O (form III) and non-dried sample α-CD$\cdot$7.6H_2O (form III) at 200 Hz.

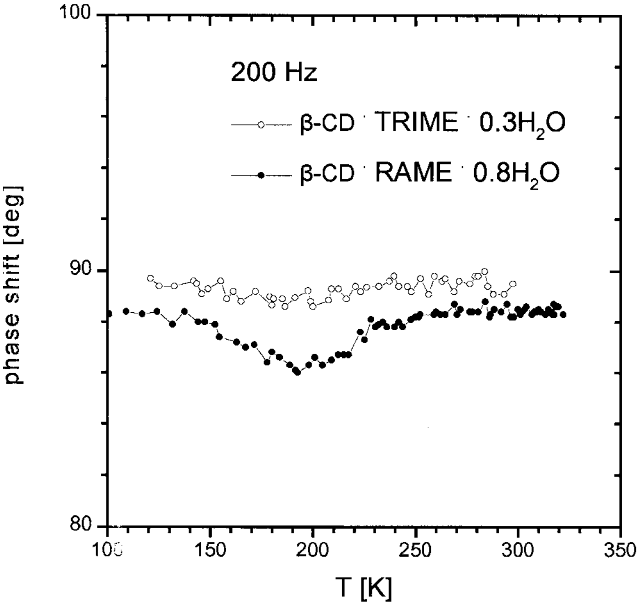

Figure 6. Temperature dependence of phase shift of the samples of β-CD$\cdot$TRIME$\cdot$0.3H_2O and β-CD$\cdot$RAME$\cdot$0.8H_2O at 200 Hz.

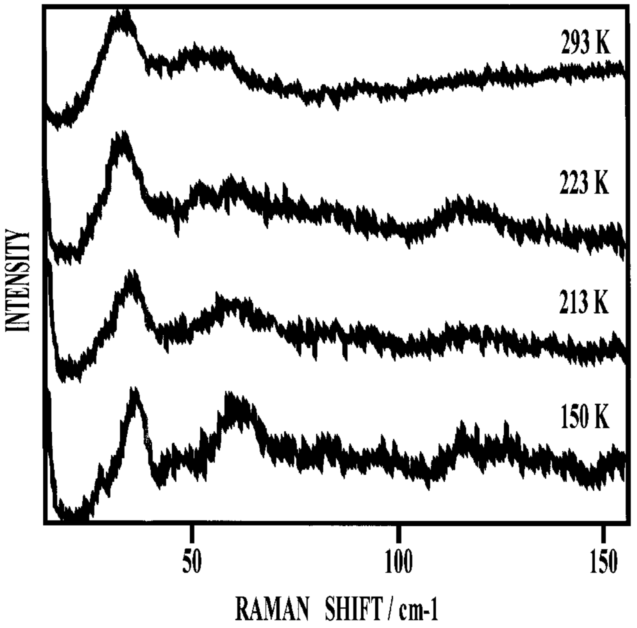

Figure 7. Low frequency Raman spectra of β-CD$\cdot$2.4H_2O at various temperatures.

has a step-like form from 33.7 cm^{-1} to 36.5 cm^{-1} and reveals a transition at a temperature of about 223 K (figure 8). The same results are found also for the β-CD$\cdot$9.8H_2O system. Similar spectra have been taken for α-CD$\cdot$1.1H_2O and α-CD$\cdot$5.9H_2O in which the temperature dependence of the 49.1 cm^{-1} band does not reveal any transition (figure 9). The frequency values decrease almost linearly from 51 cm^{-1} to 49 cm^{-1} as the temperature increases from 153 K to 293 K.

4. Discussion

Figures 1 and 2 show that the dielectric behaviour of α-CD form I is different from that of α-CD form III. The ε' values of dried α-CD$\cdot$1.1H_2O (form I) increase linearly with temperature and are almost the same as those of non-dried α-CD$\cdot$5.9H_2O (form I) over the temperature range 125–200 K. In α-CD form III the ε' values of dried α-CD$\cdot$2.9H_2O and non-dried α-CD$\cdot$7.6H_2O are almost equal to 5 over the temperature range 125–250 K, which is larger than the corresponding value $\varepsilon' \sim 2.9$ of α-CD form I. The fact that form III has ε' values larger than those of form I, which remain constant as the temperature is increased up to 250 K, means that α-CD form III has a constant conformation and an additional polarization relative to form I of α-CD for that temperature range. The additional polarization of α-CD form III is caused by differences in its crystal structure relative to form I [8]. In form III all six O(2)$\cdots$O(3′) type intramolecular hydrogen bonds between adjacent glucose units are formed while form I has four and form II has five intramolecular hydrogen bonds. Additionally, the intramolecular hydrogen bonds in form III are relatively stronger than those of forms I and II, because the mean O(2)$\cdots$O(3′) distances between

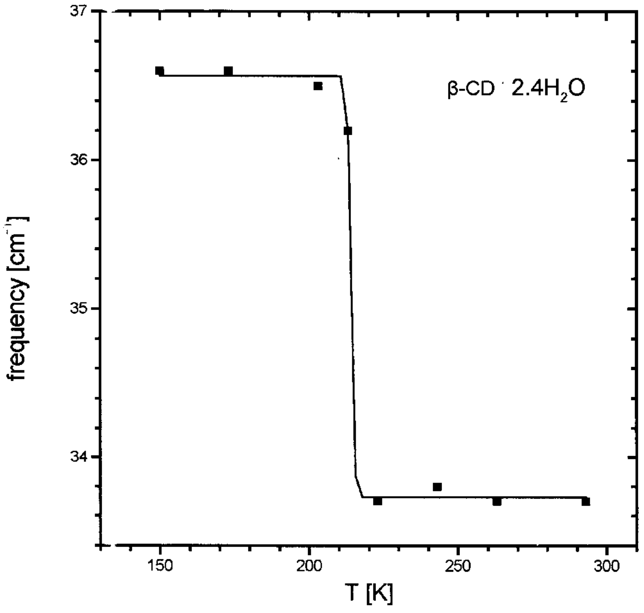

Figure 8. Temperature dependence of the 33.7 cm^{-1} band for dried β-CD·2.4H_2O.

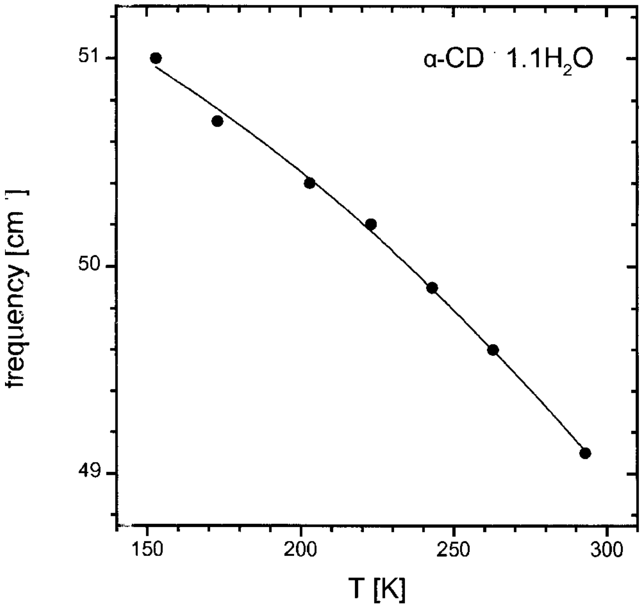

Figure 9. Temperature dependence of the 49.1 cm^{-1} band for dried α-CD·1.1H_2O (form I).

neighbouring glucose units are 3.271 Å, 3.062 Å and 2.982 Å for forms I, II and III, respectively [7]. In β-CD this is even shorter, about 2.83 Å. These distances allow relatively weak hydrogen bonds in α-CD (I or II) but strong hydrogen bonds in α-CD form III and therefore contribute significantly to the stabilization of the structure α-CD form III, which is apparent as the values of ε' are constant ~5 for $T < 250$ K. By contrast, the α-CD form I structure is not stable, and as the temperature is increased the system passes through successive conformations. The conformational change is necessarily associated with the linear dependence of ε' on temperature.

For temperatures $T > 250$ K the ε' values of dried and non-dried α-CD form III divert because of the Ω-dispersion, which depends on the number of water molecules and is significant as the temperature increases. The same happens for the system α-CD form I for temperatures $T > 200$ K.

Other characteristics of α-CD are that the ε' versus T plots do not show any single or double steps, the ε'' vs T plots (figures 1 and 2) and the φ versus T plots (figures 4 and 5) do not exhibit a transition temperature like that of β-CD [1]. This is attributed to the lack of flip-flop-type hydrogen bonds in any form of α-CD. In β-CD the seven interglucose intramolecular O(2)···O(3′) hydrogen bonds are all of the flip-flop type. Chains of these bonds are of the antidromic type [2, 3]:

$$\cdots H—O—H \cdots H—O—H \cdots H—O—H \cdots$$

The former system is equivalent to two sets of dipoles in opposite directions, and results from the average of two situations:

$$\cdots O—H \cdots O—H \cdots O—H$$

$$\cdots H—O \cdots H—O \cdots H—O$$

In α-cyclodextrin form I two of the six interglucose hydrogen bonds O(2)···O(3′) are broken and the associated glucose is rotated out of register with the other five glycoses.The former chains of these bonds are all of the homodromic type [4, 5]

$$O—H \cdots O—H \cdots O—H \cdots$$

i.e. all hydroxyls point in the same direction. The different distribution of water molecules in the three types of α-CD has no influence on the appearance of the transition temperature. It is worth noting that in the case of α-CD·7.57H_2O, where 2.57 molecules of water are disordered over 4 sites, no order–disorder transition temperature is apparent.

A second system which does not exhibit a transition temperature in the plots of ε'' versus T and φ versus T, like α-CDs, is β-CD·TRIME·0.3H_2O in which all the hydroxyl groups are methylated (figures 3 and 5). This shows the direct relation between the hydroxyl groups of β-CD and the transition temperature [1]. In β-CD·RAME·0.8H_2O with partially methylated β-CD, some of the hydroxyl groups of β-CD are not methylated, and the characteristics of the transition temperature appear again (figures 3 and 6).

The transition temperature at 223 K of the 33.7 cm^{-1} band, which is observed by Raman spectroscopy in the systems β-CD·2.4H_2O and β-CD·9.8H_2O, is related to the transition between ordered and disordered hydroxyl β-CD groups, and water molecules (or, according to Saenger, the flip-flop type hydrogen bonds are transformed to the normal type), as has been discussed [1–3]. This temperature dependence of the frequency is completely different from that expected for lattice or overall bands which are prominent in this frequency region. The observed frequency at 33.7 cm^{-1} is of the same order, as the corresponding 200 cm^{-1} calculated from the activation energy, 2.41 kJ mol^{-1}, of the transition of hydrogen bonds [1]. The 33.7 cm^{-1} frequency is also of the same order as that of the flip-flop jump rate (2×10^{10}–2×10^{11} s^{-1}), found by Steiner *et al.* [9] in their quasielastic neutron scattering measurements of β-CD·11H_2O.

The systems α-CD·1.1H_2O and α-CD·5.9H_2O do not exhibit any frequency transition with temperature like β-CD does, because of the lack of flip-flop type hydrogen bonds, as discussed in the section on dielectric spectroscopy. The linear temperature dependence of frequency, (figure 9) indicates that the structures of these systems are not stable and pass through successive conformations. By contrast, the step-like form of β-CD shows two stable conformations around the transition temperature. These results are in accordance with those of dielectric measurements.

5. Conclusion

The dielectric behaviour of dried samples α-CD·1.1H_2O (form I), α-CD·2.9H_2O (form III) and non-dried samples α-CD·5.9H_2O (form I), α-CD·7.6H_2O (form III) are described well by Debye-type relaxation (α-dispersion) and exhibit an additional Ω-dispersion in the low frequencies. The systems β-CD·TRIME·0.3H_2O, β-CD·RAME·0.8H_2O exhibit only α-dispersion.

The fact that α-CD form III has ε' values larger than those of α-CD form I is due to the different numbers and different strengths of the intramolecular hydrogen bonds. In form III all six $O(2)\cdots O(3')$ intramolecular hydrogen bonds between adjacent glucose units are formed and are relatively strong, because the mean $O(2)\cdots O(3')$ distance is 2.982 Å [7]. Form I has four and form II has five intramolecular relatively weak hydrogen bonds (mean $O(2)\cdots O(3')$ distances are larger, 3.271 Å and 3.062 Å, respectively) [7]. The fact that an OH group is more polarized if engaged in strong hydrogen bonds explains the large ε' values of α-CD form III. Additionally, form III has a stable conformation which is displayed by the constant values of ε' over the temperature range 125–250 K. By contrast, in form I, the ε' values increased linearly with temperature, indicating that the system has passed through successive conformations.

The temperature dependence of ε'' and φ in specimens all of α-CD forms I and III does not reveal any order–disorder transition, because the hydrogen bonds are not of the flip-flop type in these crystal structures [5–7]. The same happens also in fully methylated β-CD·TRIME·0.3H_2O, in which all the hydroxyl groups of β-CD are substituted with methyl groups. Since both dried β-CD·2.4H_2O and non-dried β-CD·9.8H_2O samples reveal an order–disorder transition [1] which disappears with the methylation of hydroxyls of β-CD, there is a direct relation between the hydroxyl groups of β-CD and the order–disorder transition. In û-CD·RAME·0.8H_2O, some hydroxyl groups of β-CD are not methylated, and the characteristics of an order–disorder transition are again found.

Finally, the order–disorder transition in dried β-CD·2.4H_2O and non-dried β-CD·9.8H_2O and the absence of such a transition in dried α-CD·1.1H_2O and non-dried α-CD·5.9H_2O are also shown by Raman spectroscopy.

Investigations are in progress by Raman spectroscopy of dried α-CD·2.9H_2O (form III), non-dried α-CD·7.6H_2O (form III), β-CD·TRIME·0.3H_2O and β-CD·RAME·0.8H_2O.

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