Journal of Inclusion Phenomena **5** (1987), 325–333.

Calorimetric Study of β-Cyclodextrin Undecahydrate

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(Received: 14 July 1986; in final form: 11 November 1986)

Abstract. Heat capacities of crystalline β-cyclodextrin undecahydrate have been measured in the temperature range between 13 and 300 K by use of a miniaturized adiabatic low-temperature calorimeter. A first-order phase transition occurred at 226 K with a discontinuous entropy change of 45.0 ± 1.0 J K^{-1} mol^{-1}. The highly disordered nature of the high temperature phase was considered in relation to the entropy contribution. A glass transition phenomenon observed around 150 K was ascribed to the freezing of a configurational change of the protons engaged in the four-membered hydrogen-bonded ring which appeared only in the low temperature phase.

Key words: β-Cyclodextrin undecahydrate, phase transition, entropy of transition, glass transition.

1. Introduction

Cyclodextrins [CD] can accommodate [1] guest molecules of suitable size in their central cavities, thereby forming inclusion complexes which can be obtained in crystalline form. If they are crystallized from aqueous solutions, the corresponding hydrate crystals are produced with water molecules included inside the cavities and also located in interstices between the cyclodextrin molecules. Hydrophobic, van der Waals, dipolar interactions, conformational strain, and hydrogen bonding energy have been discussed [2] as the driving forces of the complex formation. This kind of energetic consideration is important in crystalline α-CD hexahydrate which has well-defined hydrogen bonds in linear and circular arrangements [3]. In addition, entropy considerations become important in the case of β-CD hydrate crystals which are found to have a considerable disorder in the positions and orientations of water molecules and hydroxyl groups of β-CD in the room temperature structure [4,5]. The associated entropy will contribute substantially to the stability of the complex produced.

β-CD crystallizes from water as chunky prisms. The first X-ray structural analysis was done on β-CD dodecahydrate [4]. Later we reported the existence of the undecahydrate [5] in addition to the dodecahydrate. The structural difference between them is found mainly in the distribution of the disordered water molecules in the β-CD host cavity. Of course, these disordered arrangements of the constituting molecules cannot be an equilibrium structure at zero Kelvin in view of the third law of thermodynamics. Actually we found a first-order phase transition [5] at 226 K for the undecahydrate by a preliminary DTA experiment. It is the purpose of this research to measure the heat capacity and to examine quantitatively the ordering process of the highly disordered β-CD undecahydrate crystal.

2. Experimental

2.1. SAMPLE

The sample of β-CD undecahydrate was kindly donated by Professor T. Fujiwara of our University. The method of preparation was described in detail in the previous report [5]. The water content, n, of the sample was first determined by an elemental analysis, which gave the result $n = 10.5 \pm 0.5$. A gravimetric method was found to give the more accurate determination of the water content. A weighed sample was carefully evacuated in a vessel whose temperature was slowly increased up to 60 °C, until the dehydrated sample gave a constant weight. Three determinations were $n = 10.83 \pm 0.02$, 10.96 ± 0.04, and 10.94 ± 0.05, respectively. Thus, an almost stoichiometric specimen was obtained for the calorimetric study. The molar mass was taken as 1333.21 g mol^{-1}.

2.2. CALORIMETRY

A sample mass of 3.8375 g corresponding to 2.8783 m mol was sealed in a gold-plated copper cell of 5 cm^3 capacity, together with helium gas at atmospheric pressure and room temperature. The temperature of the sample cell was measured with a platinum resistance thermometer with an automatic resistance bridge (*AΣΛ*, type F17-A, England). The calorimeter, cryostat and calorimetric operation for small samples have been described earlier [6]. The temperature measurement was based on the IPTS-68 (International Practical Temperature Scale of 1968).

In addition to the conventional use of the adiabatic calorimeter for the determination of the heat capacity, enthalpy, and entropy, it can be used as an ultra-low frequency spectrometer [7]. A brief description is given here for those who need only a cursory knowledge of the principle. The heat capacity determination with a discontinuous heating mode consists of two periods: heating and equilibration periods. In the first period, the sample cell is heated to raise its temperature by 1 ~ 2 K. This energizing period is followed by the equilibration period, in which the sample temperature is measured as a function of time. The first 1 ~ 2 min of this period is required for the sample cell to reach a uniform temperature distribution. Then the calorimetric temperature drift observed for the later part of the period reflects the combined effect from a small heat leakage due to incomplete adiabaticity and from any enthalpy relaxation that the sample might show. The former is linear in time and can be corrected for by the extrapolation of the temperature-time curve. Nonlinear temperature drift that persists longer than a few minutes means that the sample relaxes from a nonequilibrium to an equilibrium state. The analysis of the relaxation process from the observed drift rate in terms of configurational enthalpy has been described previously [8].

3. Results and Discussion

The molar heat capacities of β-CD undecahydrate are listed in Table I and reproduced graphically in Figure 1. Two anomalous regions were observed. A sharp heat capacity peak centered at 226 K is due to the first-order phase transition which is characterized by the extended region of excess heat capacities on the low temperature side. The transition temperature at which the heat capacity reaches maximum value is denoted as T_{trs} in the figure. The other anomaly is a more subtle one with a slight increase of heat capacity around 150 K. The thermal relaxation behaved anomalously in the temperature range between 120 and 170 K. The temperature drift rate observed in the equilibration period is drawn in Figure 2. Here, the dashed line illustrates the estimated drift rate due to incomplete adiabatic control. The negative value corresponds to heat leakage from the calorimetric cell to the surroundings.

An exothermic temperature drift started to appear around 120 K, and became endothermic above 154 K. It returned to the normal behavior around 170 K. In the anomalous region, the spontaneous exothermic drift was treated in the same way as those due to heat leakage. The heat capacity thus calculated corresponded to the instantaneous heat capacity to which the

Table I. Molar heat capacities of β-CD undecahydrate crystal

T/K	C_p/J K^{-1} mol^{-1}	T/K	C_p/J K^{-1} mol^{-1}	T/K	C_p/J K^{-1} mol^{-1}
Series 1		99.67	621.0	214.97	1494
15.68	36.0	101.72	633.6	217.25	1535
16.65	42.4	104.04	649.1	219.51	1591
17.92	49.4	106.31	664.8	221.74	1744
18.92	55.7	108.54	679.1	223.78	2495
19.83	61.8	110.74	692.4	225.55	3312
20.90	68.9	112.91	705.9	227.41	2109
22.00	75.8	115.04	719.5	229.56	1589
23.10	83.1	117.15	733.2	231.84	1598
24.21	91.5	119.22	746.0	234.11	1609
25.35	99.7	121.29	758.9	236.37	1623
26.52	107.8	123.36	771.9	238.61	1637
27.66	115.9	125.43	788.2	240.85	1652
28.97	125.9	127.51	797.5	243.07	1667
30.42	136.7	129.59	811.3	245.29	1683
31.81	147.3	131.68	823.8	247.49	1698
33.15	157.5	133.77	837.3	249.69	1714
34.45	167.4	135.87	850.2	251.87	1730
35.85	178.3	137.97	864.0	254.04	1746
37.30	188.9	140.08	877.2	256.21	1762
38.75	199.9	142.20	890.2	258.36	1778
40.24	210.8	144.32	904.2	260.50	1794
41.69	221.4	146.45	917.4	262.64	1809
43.11	231.7	148.58	931.4	264.76	1825
44.81	244.7	150.72	945.7	266.87	1840
46.87	260.2	152.87	961.0	268.98	1854
48.96	275.8	155.01	977.5	271.08	1869
50.96	290.7	157.16	994.1	273.16	1884
52.88	305.0	159.32	1011.2	275.24	1900
54.74	318.5	161.48	1029.2	277.31	1915
56.55	332.0	163.64	1045.8	279.37	1931
58.32	345.3	165.81	1063.0	281.43	1947
60.27	359.3	167.99	1078.7	283.47	1963
62.38	373.5	170.17	1094.8	285.51	1980
64.44	387.5	172.36	1112.6	287.54	1997
66.47	401.3	174.55	1128.7	289.56	2015
68.46	414.9	176.75	1145.2	291.57	2031
70.42	428.8	178.96	1162.4	293.57	2046
72.36	442.5	181.17	1178.9	295.56	2060
74.27	455.2	183.39	1195.8	297.55	2076
76.17	467.8	185.61	1213.3	299.53	2093
78.06	483.4	187.84	1230.2		
79.93	493.0	190.7	1248.0	*Series 2*	
81.80	505.0	192.31	1266.5	121.70	762.1
83.65	516.5	194.56	1285.0	123.74	774.6
85.49	530.2	196.81	1304	125.75	787.5
87.30	541.0	199.07	1323	127.74	799.6
89.12	551.5	201.33	1342	129.70	812.3
90.95	564.3	203.60	1363	131.65	824.2
92.74	576.5	205.87	1384	133.58	836.8
94.51	587.6	208.14	1408	135.49	848.8
96.24	600.0	210.41	1434	137.39	860.3
97.94	610.9	212.70	1463	139.27	872.3

Table I. (continued)

T/K	C_p/J K^{-1} mol^{-1}	T/K	C_p/J K^{-1} mol^{-1}	T/K	C_p/J K^{-1} mol^{-1}
141.14	883.9	164.37	1051.8	193.55	1275.4
142.99	895.5	166.26	1066.5	210.25	1433
144.83	907.8	168.13	1080.2	212.88	1467
146.76	920.0	169.98	1094.2	222.58	1944
148.79	934.0	171.83	1108.5	232.18	1600
150.79	948.5	173.65	1122.7	234.61	1622
152.79	963.6	176.39	1135.5	206.97	1395
154.75	980.0	177.29	1149.5	209.21	1420
156.71	995.3	183.09	1193.4	211.86	1451
158.65	1009.7	185.74	1214.1	214.38	1486
160.57	1024.9	188.37	1234.1	216.85	1527
162.48	1038.6	190.97	1254.9		

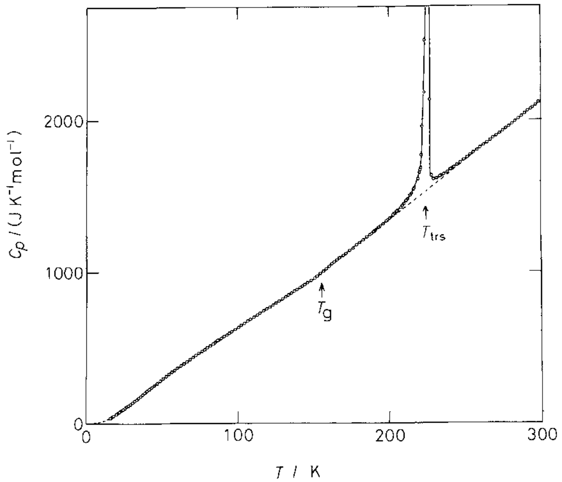


Fig. 1. Molar heat capacity of β-CD · 11H_2O. The temperature at which the heat capacity reaches its maximum value is denoted as T_{trs}.

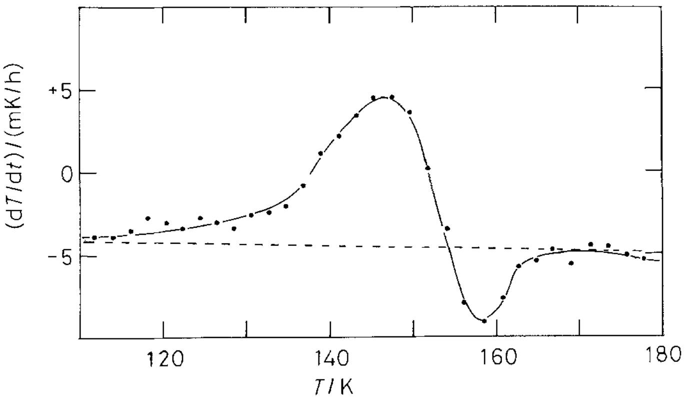


Fig. 2. Rate of spontaneous temperature change of the calorimeter loaded with β-CD · 11H_2O.

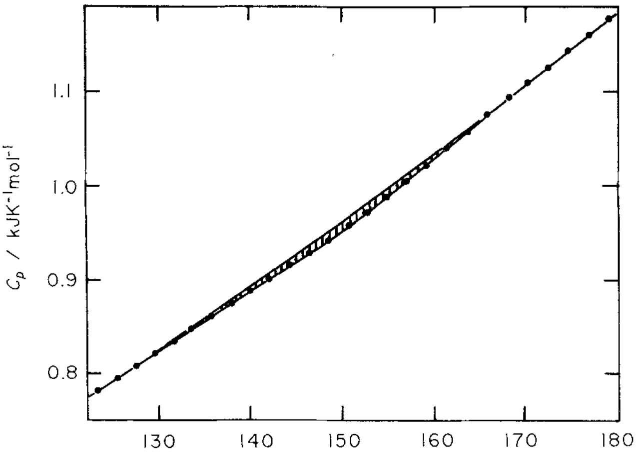


Fig. 3. Molar heat capacity of β-CD · $11H_2O$ around the glass transition temperature.

slowly relaxing part of the enthalpy did not contribute. In the endothermic region, the relaxation time became increasingly short as the temperature was raised, so that the slowly relaxing part could be, at least partly, included in the calculated heat capacity. The heat capacity data in this region is produced in Figure 3 on an enlarged scale. A simple extrapolation of the high temperature data of this figure to the low temperature side gave an estimated equilibrium heat capacity which would be obtained in an equilibrium cooling-off experiment.

These observations are quite similar to the case of crystalline $SnCl_2 \cdot 2H_2O$ [8]. Most of the disorder existing in the high temperature phase can be removed at the phase transition temperature on cooling. However, a part of the disorder survives in the low temperature phase. The ordering of the remaining disorder proceeds in a continuous way as the temperature is lowered and freezes at a certain temperature at which the relaxation time for the ordering process crosses the time scale of the single heat-capacity determination.

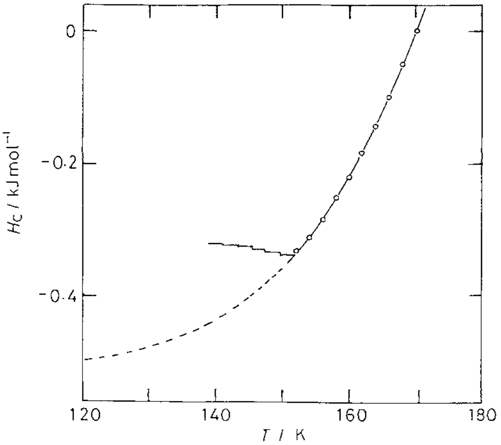


Fig. 4. Temperature-enthalpy relation of β-CD · $11H_2O$ around the glass transition temperature. The zig-zag line indicates the path followed by the crystal in this particular measurement.

In order to derive kinetic parameters for the relaxational behavior from the experiment, the temperature drift rate was integrated to give the enthalpy-temperature relation of the crystal. This is shown in Figure 4, where the dashed line is an expected equilibrium enthalpy curve below the glass transition temperature T_g. This was calculated by integrating the extrapolated heat capacity values. The reference temperature of the enthalpy is chosen arbitrarily as 170 K. The zig-zag chain is the path which the configurational enthalpy H_c of the crystal followed during the heat capacity measurement after cooling. The almost horizontal parts of the curve correspond to the heating period, while the almost vertical parts belong to the equilibration period. These are typical of the irreversible process of the glass transition. Of course, this behavior is not a unique representation of the intrinsic property of the crystal but depends on the experimental time scale: the cooling rate and the time spent on the measurement. By assuming an exponential approach of the configurational enthalpy towards the equilibrium value at respective temperatures with a single characteristic time, the relaxation time τ was calculated from the observed temperature drift rate dT/dt and the heat capacity C by the following equation.

$$\frac{dH_c(T,t)}{dt} = -\frac{H_c(T,t)}{\tau} = -C\frac{dT}{dt}$$

The relaxation time τ is shown in Figure 5 in the Arrhenius form. The activation enthalpy thus determined is 47 ± 2 kJ mol^{-1}.

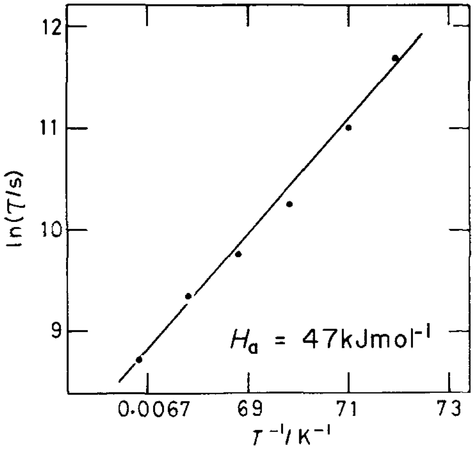
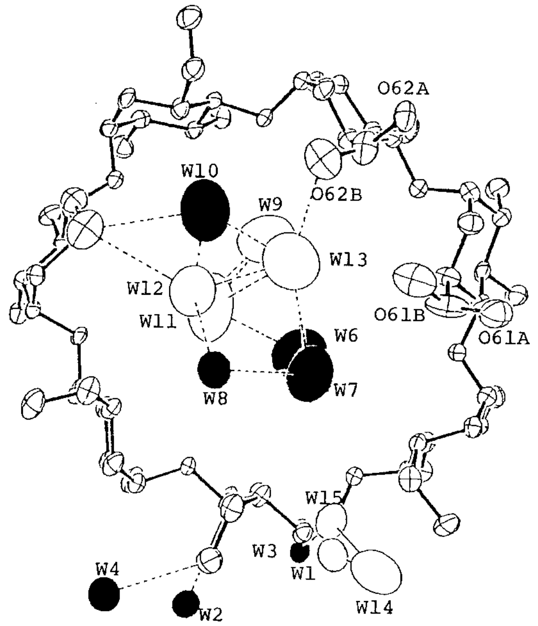


Fig. 5. Arrhenius plot of the enthalpy relaxation time τ of β-CD · 11H_2O.

We have developed a least-squares fitting program [9] for the determination of the so-called 'normal heat capacity' which provides a basis for the derivation of the enthalpy and entropy of the transition. The freezing phenomenon observed around 150 K gives a good basis for the low temperature data of the normal heat capacity. In the absence of the necessary information required for the method, like intra- and inter-molecular vibrational frequencies, however, we are forced to obtain the normal heat capacity by connecting simply the heat capacity data below 200 and above 230 K. This is shown in Figure 1 by the dashed line. The corresponding entropy change, 45.0 ± 1.0 J K^{-1} mol^{-1}, does not include the continuous part of the excess entropy and is a minimum value for the entropy of transition.

In this crystalline hydrate, there are many hydrogen bonds which are formed between water molecules and hydroxyl groups (one primary and two secondary OH groups per glucose). The hydrogen bonding network contains several infinite chains running through the whole crystal. The chains can also close up circularly with four to seven hydroxyl and water molecules. A complication arises from the disorderd nature of some oxygen atoms of the water molecules and hydroxyl groups: In this respect, it is necessary to describe briefly the crystal structure. Figure 6 shows a schematic drawing of the disordered structure of β-CD undecahydrate at room temperature. The X-ray study [5] has shown that the 11 water molecules are statistically distributed over 15 positions, of which only 6 (waters W5, W6, W7 inside the cavity and waters W3, W4, W8 outside the cavity) are fully occupied. The others are distributed over several positions with fractional occupancy in the range 0.16 ~ 0.94. The occupancy of the water molecules is indicated in Figure 6. Moreover, some of the hydroxyl groups O(61) and O(62) have two possible positions, A and B which are almost half-filled. Disorder can be correlated with the entropy of the system through the Boltzmann relation. The entropy due to the positional disorder is given by $-R\sum_i f_i \ln f_i$, where f_i is the fractional occupancy of an oxygen atom at the ith site and R is the gas constant. The corresponding entropy with the tabulated occupancy fraction f amounts to 32.3 $\mathrm{J\ K^{-1}\ mol^{-1}}$ in total. Of course the two kinds of disorder pertaining to the waters and hydroxyls cannot be independent of each other. The two kinds of oxygen will move in a concerted manner owing to the repulsion and this restriction operates to reduce the associated entropy. However, the interrelation is too complicated to be taken into consideration properly. The calculated entropy, therefore, corresponds to a maximum value.



The water inside the cavity	*f*
W 5	1.00(3)
W 6	1.00(4)
W 7	1.00(3)
W 9	0.70(3)
W10	0.90(3)
W11	0.62(4)
W12	0.39(3)
W13	0.64(4)
The water outside the cavity	
W 1	0.64(3)
W14	0.20(3)
W15	0.16(3)
W 2	0.94(2)
W 3	1.00(2)
W 4	1.00(2)
W 8	1.00(2)
Disordered O 6	
O61A	0.42(3)
O61B	0.58(3)
O62A	0.58(2)
O62B	0.42(2)

Fig. 6. Schematic drawing of the disordered structure of β-CD · $11H_2O$ at room temperature with the occupancy fraction f of oxygen atoms of waters and hydroxyl groups. The water W5 is located just behind the water W12 in this drawing.

The second aspect of disorder comes from the proton positions. According to the neutron diffraction studies [10], there are 35 hydrogen bonds in β-CD undecahydrate, of which 17 have the ordered proton arrangement. The remaining 18 are of a statistically disordered nature with double minimum potential. In the latter, oxygen atoms are separated by normal distances in the range 270 ~ 300 pm, and the associated proton positions are filled with occupation fractions adding up to 1. Saenger *et al.* [11] gave a nomenclature 'flip-flop' to this kind of hydrogen bond. The nature of the proton disorder has been extensively studied for hexagonal ice. The residual entropy of ice was explained by Pauling [12] in terms of the half-hydrogen statistical model subject to the ice conditions originally proposed by Bernal and Fowler [13]. Pauling calculated the associated entropy due to the disordered protons in ice to be $(k/2)\ln(3/2)$ per hydrogen bond by a simple and ingenious way. Here, k is the Boltzmann constant. The disorder is believed to be frozen-in owing to the prolonged relaxation time at low temperature before the crystal reaches a hypothetical transition temperature at which the disordered proton system would have an ordered configuration. The phase transition was actually observed in KOH-doped ice at 72 K [14] for ordinary ice and at 76 K [15] for heavy ice. The dopant was believed to accelerate the rate of change in proton configuration by creating an ionized vertex with an orientational defect.

The entropy due to the proton disorder was calculated to a higher approximation [16] in the case of ice for which the high crystallographic symmetry requires disorder of this kind with proton positions exactly half-occupied. In β-CD undecahydrate, no such restrictions apply and all hydrogen bonds of the flip-flop type are formed without symmetry constraints. If we assume that Pauling's approximation be applied on average to the present hydrogen-bonded system at it stands, the entropy associated with the proton disorder amounts to $30.1\ \mathrm{J\,K^{-1}\,mol^{-1}}$ [$= 18 \times (R/2)\ln(3/2)$]. Comparing the experimental value of the entropy of transition to the sum of the calculated values based on the room temperature structure, and considering the involved approximate nature of both values, we are apt to believe that the low temperature phase is almost completely ordered. This conjecture was actually confirmed by a recent neutron diffraction study [17]. The diffraction experiment made at 120 K showed that almost all the water molecules and hydroxyl groups as well as protons were fully ordered. The most remarkable feature in the crystal structure of β-CD undecahydrate at 120 K is the existence of a four-membered hydrogen-bonded ring in which protons of a statistical nature are involved. This four membered ring appeared only in the low temperature phase and was formed between O(24), O(35), O(W2), and O(W7) in their nomenclature of the low temperature phase. The new formation may be due to an energetical advantage at the low temperature over an entropy advantage at the high temperature. Zabel and Saenger called it a quadratic 'flip-flop' hydrogen-bonded system because there are two protonic configurations in the ring: clockwise and anti-clockwise arrangements. Both of the arrangements can be converted to each other by a synchronized oscillation. However the dynamical nature of the coupled proton motion is a matter of concern.

A similar four-membered hydrogen-bonded ring was observed to exist in Na_2SO_4 decahydrate crystal [18]. There is one such ring for each formula unit, and the two possible ways of arranging the protons in completely random ways lead to an entropy of disorder of $R\ln 2$, in agreement with the residual entropy experimentally observed [19]. This means that the coordinated movement of the protons freezes at low temperature before the crystal reaches a hypothetical transition temperature which depends on the energy difference associated with the two possible arrangements in the crystal. Thus, the glass transition behavior of the present hydrate crystal observed around 150 K will be correlated with the frozen-in disorder of the two configurations of protons engaged in the four-membered hydrogen bonds.

Many hydrogen-bonded crystals have been found to exhibit glass transition phenomena by a careful calorimetric measurement. They are $SnCl_2 \cdot 2H_2O$ [8], H_3BO_3 [20], pinacol hexahydrate [21], H_2O [22], and their deuterated analogues. In all of them, the freezing of proton configurations in respective hydrogen-bonded networks was believed to be the main reason for the glass transition. The activation enthalpy governing the relaxational process is in the range $22 \sim 88$ kJ mol^{-1}. The glass transition takes place in the temperature range between $110 \sim 300$ K. Therefore, the reasoning that the glass transition of β-CD undecahydrate is due to the freezing of the proton configuration is not an uncommon case. In this respect, the deuteration effect on the freezing behavior deserves further study.

Acknowledgements

This research was supported financially by the Grant-In-Aid for the Special Project Research on the Properties of Molecular Assemblies (No. 58118007) from the Japanese Ministry of Education, Science and Culture. The authors express their sincere thanks to Prof. T. Fujiwara for his kind donation of the present sample. Thanks are extended to Prof. W. Saenger of Berlin Free University for sending a preprint of their low-temperature neutron diffraction work.

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