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Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Hydration Structures of Lactic Acid: Characterization of Ionic Clathrate Hydrate Formed with a Biological Organic Acid Anion

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Ionic clathrate hydrates are water-based materials that have unique properties, such as a wide range of melting temperatures and high gas capacities. In the structure, water molecules coordinate around ionic substances, which is regarded as the actual hydration structure and also linking of the hydrate clusters, giving insight into the dynamics of the water molecules and ions. This paper reports synthesis and characterization of the ionic clathrate hydrate of tetra-*n*-butylammonium lactate (TBAL), the anion of which is a biological organic material. Phase equilibrium measurements and optical observations of the crystal morphology and crystal structure analysis were performed. The TBAL hydrate has 284.8 K of melting temperature suitable for cool energy storage applications. The actual hydration patterns around a lactate anion are shown in the form of ionic clathrate hydrate structure.

Introduction

Improving energy efficiency is a key to sustainable development and finding a solution to energy and environmental issues. Thermal energy storage technologies use renewable and/or excess energies, e.g., day and night temperatures, solar heat, and excess electricity.[1] Ionic clathrate hydrates (ionic salt hydrates) have great potential for low-temperature energy storage. Although these materials mostly consist of water, the melting temperatures are in a wide range from 273 to 300 K. Therefore, they can be used for air conditioning of living environments.[2–4] Taking advantage of their thermodynamic stability with large storage capacity, many potential gas applications have also been proposed, such as carbon capture and hydrogen storage.[5–10]

Ionic clathrate hydrates, are crystalline guest–host materials that consist of water (host) and an ionic guest substance.[11–12] Tetra-*n*-butylammonium (TBA) and -phosphonium (TBP) salts have a strong tendency to form ionic clathrates because of the excellent compatibility of the cations with hydrate cages.[13–16] The crystal structure of ionic clathrates is similar to that of canonical clathrate hydrates, in which the water molecules form a cage-like hydrogen-bonding network and the guest molecules, such as CH_4, CO_2, and N_2, are encapsulated in the pentagonal dodecahedral (D) cage.[17] Because the melting temperatures of the TBA and TBP salt hydrates can be controlled from 273 to 300 K by selecting various anions, they are suitable media for cool energy storage.

As well as energy storage media, the ionic clathrate hydrates can also be used to know the actual hydration structure of the anion in the form of a crystal structure. The hydration structure of biochemical substances in aqueous solution provides important information about enzymatic reactions, protein binding, and ion reactions in the atmosphere.[18–22] As an ionic guest substance, the TBA and TBP cations have various options for the counter anion, e.g., carboxylates. Lactic acid is an alpha-hydroxy acid that is currently used and being developed for many applications because of good bioavailability and biodegradability,[23–25] and the lactate anion is a candidate for the ionic guest anion. In the spectroscopic or spectrometric measurement, information is limited for the qualitative signal or cluster size.[18,26] The crystal structure analyses of these hydrates can directly reveal the actual hydration structure and also linking of the hydrate clusters, giving insight into the dynamics of the water molecules and ions. The anions can modify the hydrate structure as a result of hydrogen bond interactions between lattice water molecules and hydrogen bonding groups of the anion, such as hydroxyl and carboxyl groups. In the ionic clathrate structures, TBA carboxylates, e.g., formate, acetate, and propionate, show more complex clathrate structures than halogenated ionic clathrate hydrates.[13–16,27–30] The organic acid anions can occupy empty cages, and the oxygen atoms of the anion likely form hydrogen bonds with the water molecules in the cage lattice.

Herein, we report characterization of the ionic clathrate hydrate of TBA lactate (TBAL), which is considered to be more compatible with biological environments than typical ionic guest compounds. Phase equilibrium measurements and optical observations of the crystal morphology and crystal structure analysis were performed. The TBAL hydrate has 284.8 K of melting temperature close to that of TBAB hydrate. Two different crystal morphologies were observed, and one was characterized by single-crystal X-ray diffraction. The lactate anion occupied the D cage hydrogen bonding between the cage lattice water at the carboxyl and also hydroxyl groups.

Experimental

Materials

The raw material used in the experiments was deionized and distilled water. TBAL aqueous solution was synthesized by neutralization of L-(+)-lactic acid (90 mass% solution in water, Acros Organics b.v.b.a., Belgium) with tetra-*n*-butylammonium hydroxide (40 mass% solution in water, Alfa Aesar Inc.). The base was added to the acid while monitoring the pH with a pH meter which finally became ~7.

Phase equilibrium measurements

In this paper, we defined the molar fraction x as of the molar fraction of the TBA cation to the lactate anion in the mixture. We prepared 14 aqueous solutions with different molar compositions from x = 0.0029 to 0.0412 (0.050–0.442 in mass fraction). We injected 2 g of the sample solution into a test tube. The test tubes were set in a water bath thermostated by a cooling water circulator. The system temperature was measured by a platinum resistance thermometer. Initially, all of the samples were crystallized by decreasing the system temperature to ~268 K. We then increased the system temperature with a step of 0.1 K while observing crystal dissociation. The dissociation lasted for 14 days in the longest case. To check the state of the crystals, we optically monitored the samples using a digital microscope with 0.1-mm resolution. When the crystals in the test tube completely dissociated, the system temperature before that step, i.e., 0.1 K less than the current temperature, was determined to be the equilibrium temperature for the aqueous TBAL composition. The details of the measurement method are described elsewhere.[4,29] The measurement uncertainties were ±0.1 K for temperature and ±0.0003 for aqueous TBAL molar composition with 95% coverage.

Elemental analysis

For the elemental analysis of the cation and anion amounts in the neutralized aqueous solution, we initially prepared a dry sample using an evaporator. The mass difference between the samples in aqueous and dry conditions gave the mass fraction of ions as 0.442. After water elimination, the sample was a solid at ambient conditions. Elemental analyses (C, H, N) were performed with an automatic element analyzer (EA1110; CE Instruments, Milan, Italy) by a combustion/gas chromatography−thermal conductivity detection method. Then, 2.0–2.5 mg of the sample in a tin foil cup with 5-mm diameter and 8-mm height was incinerated under an oxygen gas stream with chromium (II) oxide and silvered cobaltous (II, III) oxide catalysts. The combustion gas was separated into nitrogen, carbon dioxide, and water with a Cu-packed column, and then they were moved to a Porapac QS packed glass column (2-m length and 5-mm i.d.) with a carrier helium gas. The separated oxidation products were detected by a thermal conductivity detector. The measurements were performed three times, and the averaged ratio of TBA to lactate was determined to be 1:1.7.

Single-crystal X-ray diffraction measurement

The single-crystal samples for the X-ray diffraction measurements were prepared by the same method as we have previously reported.[13] The sample crystals were formed from TBAL aqueous solution with x = 0.0228. The crystals were grown with ~1.5 K subcooling temperature, which enabled growth of millimeter-sized single crystals. A video of the crystal growth under the conditions of x = 0.0228 and T = 282.7 K is available in the ESI†.

Under these conditions, we obtained polygonal columnar- or needle-shaped crystals. After crystallization, we removed the crystals from the solution and transferred them to the diffractometer (Bruker AXS CCD). During handling and transfer, the sample temperature was maintained below 263 K. We collected the diffraction data at 100 K with MoK$_\alpha$ radiation (λ = 0.7170 Å). The crystal structure was solved and refined using the SHELXTL program.[31] All atoms except for hydrogen were refined with anisotropic thermal parameters. During the refinement, the complete TBA ion appeared in the fused T_3P_1 cage. In the fused T_4 cage, the cation had less symmetry, i.e., one butyl chain was originally observed and its site occupancy was divided into four chains generated by the symmetry operation. The lactate anions were found in the dodecahedral cages neighboring the cages occupied by TBA cations. The occupancies for the anions were preliminary calculated by the program, and then fixed to values that provided reasonable thermal parameters. The hydrogen atoms of the TBA ion were added by the program, while those of the water and lactate ion were located using a difference Fourier map when they were found in reasonable positions. The crystal structure refinement results are summarized as follows: $C_{19}H_{102.4}N_1O_{33.7}$, Mr = 857.28, tetragonal, a = 23.361(2), c = 12.248(2) Å, V = 6684.5(15) Å^3, T = 100 K, space group $P\bar{4}$ (no. 81), Z = 5, 11758 reflections measured, 9652 unique (R_{int} = 0.0371), which were used in all calculations. The final $R1$ and $wR(F^2)$ were 0.0792 and 0.2130 (0.0933 and 0.2231 for all data). The crystal structure was visualized by VESTA.[32] CCDC 995870 contains the supplementary CIF crystallographic data for the crystal structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Results and Discussion

Phase equilibrium and crystal morphologies

The results of the phase equilibrium measurements are shown in Table 1 and Fig. 1. The freezing point depression effect was observed during the measurement for the sample with x = 0.0029, where the hydrate crystal was stable only below the ice point. The melting temperature greatly increased up to the composition x = 0.0190. The slope of the melting temperature curve then decreased and became constant at T = 284.8 K for x = 0.0297 and 0.0326. The T–x curve then showed a decrease of 0.5 K from x = 0.0326 to 0.0412.

During the measurements, we observed two different crystal morphologies, i.e., rectangular columnar and polyhedral crystal shapes which are shown in Fig. 2. The former was observed at all compositions except for the sample with x = 0.0353. The dominant crystal morphology is shown in Fig. 2A and 2B, which were observed at x = 0.0161 and 0.0228 (sample for the X-ray diffraction measurement), respectively. They had rectangular columnar shape and grew rapidly in one direction. For the samples with x = 0.0326 and 0.0353, the other crystal

Table 1 Results of phase equilibrium temperature measurements.

Mole fraction ($\times 10^{-2}$)	Mass fraction	Temperature (K)
0.29	0.050	272.6
0.61	0.101	275.4
0.96	0.151	278.5
1.36	0.203	281.0
1.61	0.232	282.2
1.90	0.263	283.3
2.09	0.282	283.8
2.29	0.302	284.1
2.51	0.322	284.5
2.74	0.342	284.7
2.97	0.360	284.8
3.26	0.383	284.8
3.53[a]	0.402	284.5
4.12[a]	0.442	284.3

[a] The most stable crystal had a polygonal shape.

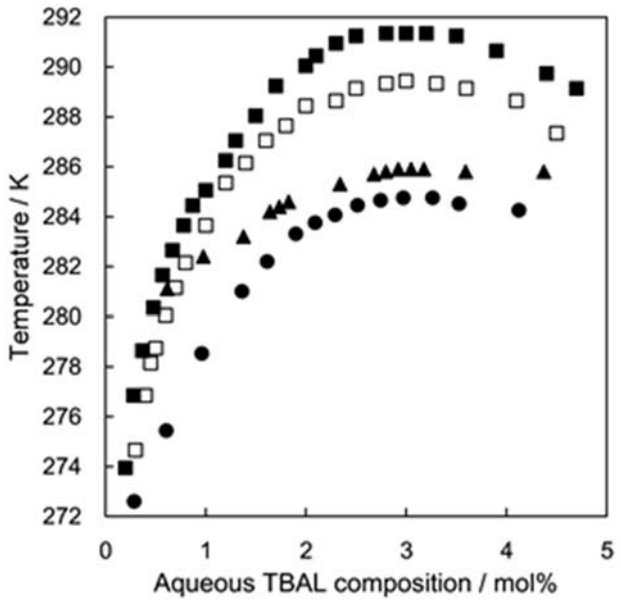

Fig. 1 Phase equilibrium conditions for TBAL ionic clathrate hydrate: ●, this work; ■, TBA propionate hydrate[27]; □, TBA acetate hydrate[27]; ▲, TBAB hydrate[4].

morphology was observed, i.e., polyhedral crystals. Crystals grown at T = 284.3 K with x = 0.0326 and 0.0353 are shown in Fig. 2C and 2D, respectively. With x = 0.0326, polyhedral crystals initially appeared, but after a temperature increase of 0.1 K the crystals melted. After that, rectangular columnar crystals appeared and grew to millimeter size and then melted after a temperature increase of 0.1 K. For the x = 0.0353 sample, the rectangular-columnar-type crystals were not observed, and the polyhedral crystals melted at 0.1 K higher temperature than those of the x = 0.0326 sample. The morphology of the crystals formed from the solutions with x = 0.0353 and 0.0412 was polygonal. Therefore, the melting curves of the two phases, i.e., columnar and polygonal crystals, may cross at x = 0.0326. The melting temperature slightly decreased for x > 0.0326, probably because of the effect of excess salt fraction. The present phase equilibrium measurements and morphology observations indicate that the TBAL ionic clathrate hydrate has at least two crystal structures, and they have almost the same melting temperature and composition.

Compared with TBA acrylate, propionate, and butylate, the highest melting temperature of the present salt hydrates was ~6 K lower. This is close to that of TBAB, which is a cool energy storage medium for office air conditioning. Thus, the melting temperature was adjusted to a suitable temperature for office cooling applications. In other words, the extra hydroxyl group of the lactate anion destabilizes the hydrate structure compared with that of the TBA propionate hydrate. Discussion of the thermodynamic stability based on the crystal structures follows in the next section.

Crystal Structure

Columnar-shaped single crystals formed from the x = 0.0229 aqueous solution, as shown in Fig. 2B. The determined structure is identical to Jeffrey's type III ionic clathrate hydrate, and the chemical formula of the hydrate structure is TBAL·29.8H_2O.

The TBA cation occupied the fused T_3P_1 and T_4 cages, where T and P denote tetrakaidecahedral and pentakaidecahedral cages with pentagonal and hexagonal faces, respectively. The cation showed similar disorder to those in TBAB and TBPB.[13,29] The number of TBA cations in the T_3P_1 and T_4 cages were 4 and 1 per unit cell, respectively.

There are three symmetrically distinct D cages in the structure. The cage structure in the unit cell can be written as $4D_A{\cdot}4D_B{\cdot}2D_C{\cdot}4T_3P_1{\cdot}T_4$. The D_A and D_B cages are occupied by the lactate anion, where three water molecules in the lattice are replaced by one lactate anion. The space group was determined to be $P\bar{4}$, and that of the corresponding original Jeffrey's structure is $P4_2/m$. The different space groups is probably because of the lower symmetric ionic guest, i.e., the lactate anion. The $P\bar{4}$ space group has mirror symmetry, which is not possible for chiral molecules. Because the other possible space groups, e.g., $P4$, led to a structure with an insufficient R factor (>40%), racemization of the anion possibly occurred by the heat of neutralization.

Three configurations of lactate anion were found in the D_A cage, and one of them was the same as observed in the D_B cage. In all cases, the two carboxyl and one hydroxyl groups of the anion formed hydrogen bonds with the neighboring lattice water. They faced the TBA cation, which means that electrical neutrality was maintained in the local area in the crystal as well as in the aqueous solution. In both of the D_A and D_B cages, one water molecule was missing from the apical position of the original D cage lattice. This is because of position of the asymmetric carbon atom of the lactate anion, which is too close to the original location of the water molecule. The hydrophobic methyl group is directed toward the center of the D cage to fill the empty void space. However, because the carbon chain is restrained by the hydrogen bonded carboxyl and hydroxyl groups, the methyl group cannot reach the center of the cage.

Figure 3 shows the three possible lactate anion configurations in the D_A cage, which is fully occupied by the anion with the three configurations. In this figure, the relatively regular D cage available in the TBAB hydrate structure[30] is also drawn. It is clear that the D_A cage shape is highly distorted towards the TBA cation because the lactate anion is close to it. The hydroxyl group forms two hydrogen bonds with the lattice water, as with the case of the canonical hydrates of alcohols.[33–35] In the D_B cage, an anion

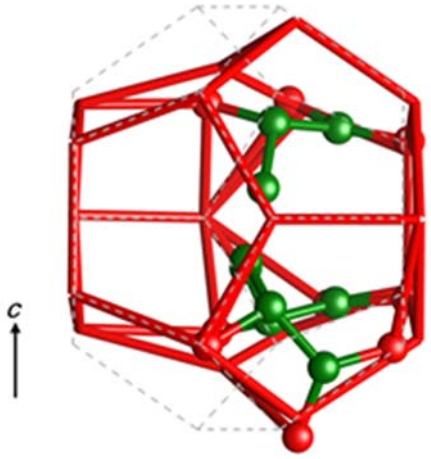

Fig. 3 The three possible lactate anion configurations in the highly squeezed D cage (D_A). Red and green indicate oxygen and carbon atoms or bonds, respectively. The atoms of the lactate anions are shown as spheres. The lattice water is only shown by bonds, and the hydrogen atoms are omitted for clarity. The dotted line shows the relatively regular D cage in the TBAB hydrate drawn with the same O–O bond lengths.[30]

configuration similar to one of the three in the D_A cage was observed. The hydration structure of a guest substance in hydrate crystals is analogous to the hydration structure in aqueous solution.[36] The present crystal structure provides a couple of detailed hydration patterns of the lactate anion including one previously undiscovered pattern.[18]

Stabilization with *Guest* Water

A *guest* water molecule is found in the D_C cage. The *guest* water molecule can occupy two symmetrically equivalent positions, and form hydrogen bonds with the lactate anions in the neighboring D_A cages. The hydrogen bond lengths between the lactate anion and the *guest* water are 2.94 and 2.75 Å, which are in the normal range of hydrogen bonds. This hydrogen-bonded network may stabilize the occupancy of the *guest* water molecule in the D-cage, as is the case with other TBA carboxylate hydrates.[15,16] Because the D_C cage is located far away from the nitrogen atom of the TBA cation, it is neither occupied nor squeezed by the anion and maintains a regular D-cage shape. Therefore, this cage is considered to be available for small gas molecules.

At the beginning of the refinement process, the site occupancy of the *guest* water was not fixed. However, it spontaneously became close to one of the three disordered anion positions. Figure 4 shows one of the possible cases in which the *guest* water has hydrogen bonds with the anions in the two neighboring D_A cages and the anions are symmetrically equivalent. This hydrogen-bonded chain structure of the lactate anion, which has not been previously reported, may replicate clustering in aqueous solution. It is also interesting that the five hydrogen bonds with one lattice water molecule are visible in Fig. 4. Because X-ray diffraction measurements give a static picture of a structure containing dynamics, the five hydrogen-bonds are considered to be averaged bond dynamics.

Here, we can suggest the reason for the lower melting temperature of the present TBAL hydrate compared with the TBA acrylate and propionate hydrates from our phase equilibrium measurements. Differing from simple carboxylates,

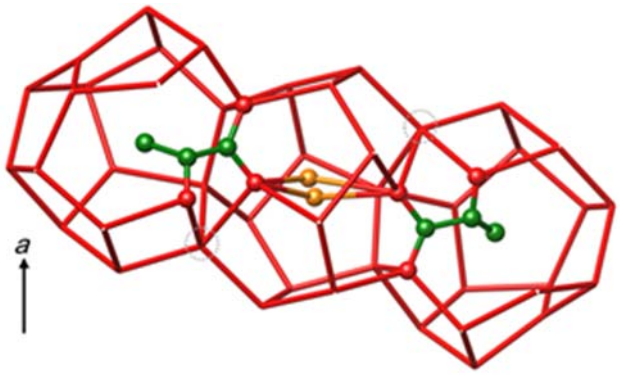

Fig. 4 Possible hydrogen-bonded chain between lactate anions and *guest* water molecules (orange) through three neighboring D cages (D_A–D_C–D_A). Two positions of the water molecule generated by a symmetry operation are shown. The dotted circle shows the water molecule with five hydrogen bonds with neighboring atoms.

the hydrophobic chain of the lactate anion is relatively short. Furthermore, one water molecule is pushed out of the lattice by the restrained asymmetric carbon atom. Therefore, the cage center is not sufficiently occupied by the guest, and the hydrate lattice is likely to be unstable. In this structure, the *guest* and *host* water molecules may contribute to stabilization of the lattice compared with other ionic clathrate hydrates. It is also expected that the *guest* water molecule can be easily replaced by small guest gas molecules, such as CH_4, CO_2, and N_2, and the structure would then be modified by the enclathration.

Differing from the known ionic clathrate hydrates, a completely empty cage was not found in the present hydrate structure, that is, all of the D cages were fully or partly occupied by the lactate anion or *guest* water molecules. The *guest* water can form hydrogen bonds with the anion. The cage occupied by the water may be available for small gas molecules. Therefore, the present material is possible for gas separation/storage technologies. A particular hydrogen-bonded chain between the two anions and one *guest* water was found in the present structure. However, the actual interactions are still unclear from our present experiments, and this should be studied by suitable methods, e.g., computational simulations and nuclear magnetic resonance measurements.

Conclusions

In this study, we synthesized an ionic clathrate hydrate of tetra-*n*-butylammonium lactate and characterized the thermodynamic stability and crystal structure. Although the melting temperature of TBAL hydrate (284.8 K) was found to be lower than those of TBA propionate (291.4 K) and acetate (289.5 K) hydrates, it is close to those of TBA formate (285.4 K) and TBAB (286.0 K), which are suitable compounds for refrigeration applications. Owing to the biodegradability and carbon neutrality of the anion, TBAL hydrate could be used in wider fields than TBA formate and TBAB, such as in the food and agricultural industries. This study provides a method to further stabilize/modify ionic clathrate hydrate structures by crystal engineering with more complicated and environmentally-friendly biochemical materials.

The lactate anion was disordered with different possible hydrogen

bonds with *host* and also *guest* water molecules. The actual hydration structures of the lactate anion were determined, and the result was consistent with that in aqueous solution measured by a spectroscopic technique. Thus, the present technique can provide detailed information to understand the role of hydrogen bonds in biological structures and reactions.

Acknowledgments

We thank Drs. Kunioka and Han for valuable discussion about the chemical properties of the synthesized substance. We also thank Drs. Gotoh and Shibasaki for technical support of the X-ray diffraction experiment and the elemental analysis. SM received a Grant-in-Aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (No. 26820069).

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† Electronic Supplementary Information (ESI) available: video of the crystal growth of the TBAL hydrate. In this video, 0.2 s corresponds to 1 h in the experiment. See DOI: 10.1039/b000000x/. CCDC 995870 contains the supplementary CIF crystallographic data for the presently determined crystal structure of TBAL hydrate. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Cite this: DOI: 10.1039/c0xx00000x

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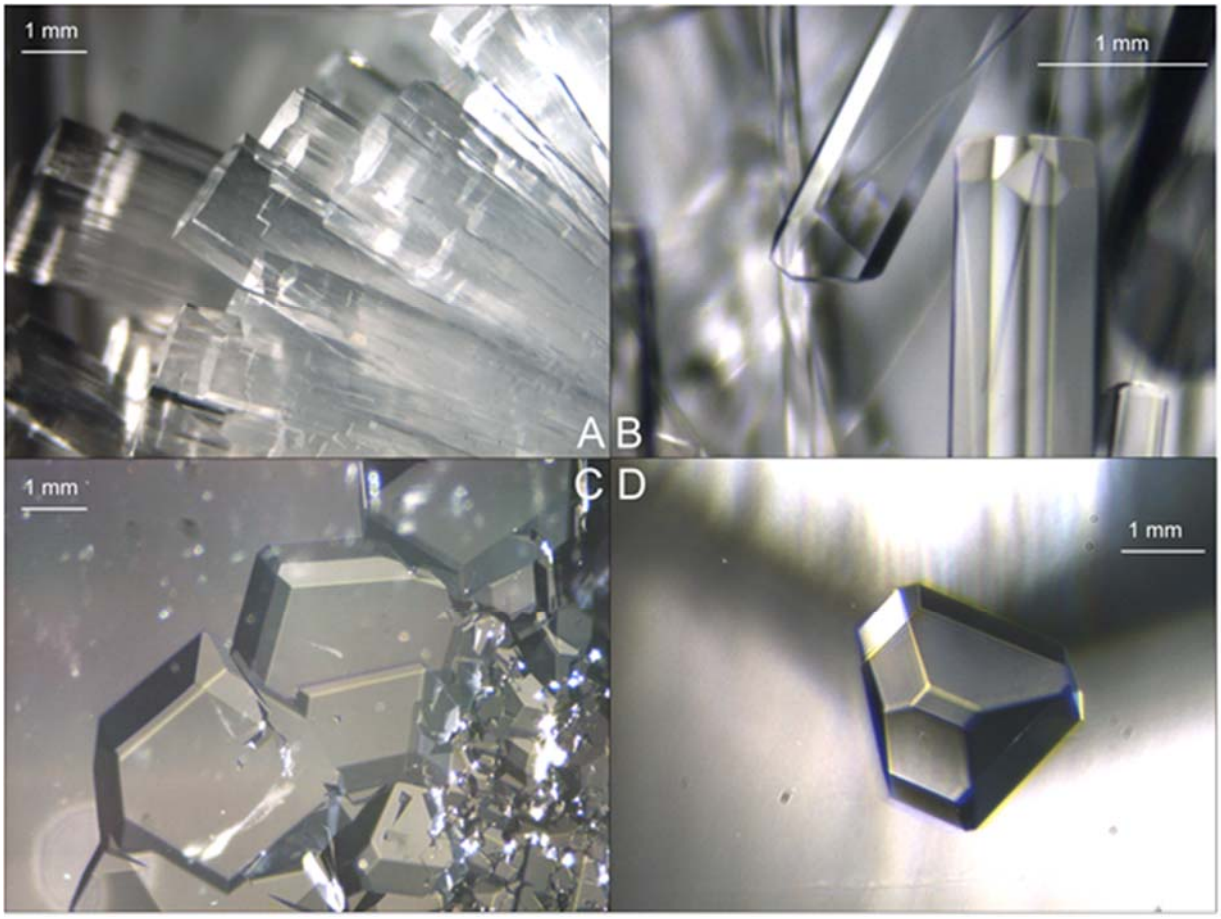

Fig. 2 Different morphologies of the TBAL hydrates. A: $x = 0.0161$, B: $x = 0.0228$ (sample for the X-ray diffraction measurement), C: $x = 0.0326$, and D: $x = 0.0353$.

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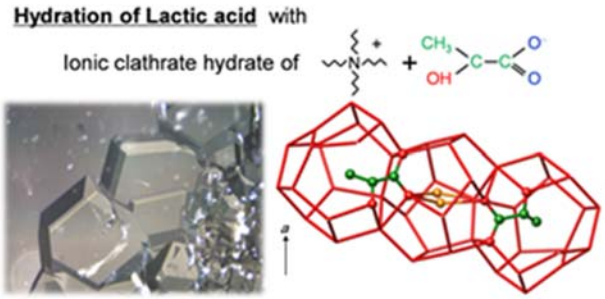
GRAPHICAL AND TEXTUAL ABSTRACT



Lactic acid is incorporated in ionic clathrate hydrate showing various water clustering patterns.