ELECTRONIC SUPPLEMENTARY INFORMATION

Insight into a direct solid-solid transformation: a potential approach to removal of residual solvents

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Materials

cAMPNa·xH$_2$O (purity >99% as anhydrous state calculation) was obtained from Biotogether (Nanjing, China) and used after recrystallization. Inorganic compounds and organic solvents of analytical grade were purchased from commercial sources and used without further purification. cAMPNa (CAS number: 37839-81-9)

Powder X-ray Diffraction (PXRD)

PXRD patterns were measured at ambient temperature on a D8 Advance (Bruker) diffractometer using copper radiation (Cu Kα) at the wavelength of 1.54059 Å, equipped with a LynxEye position sensitive detector. The tube voltage and current were set to 40 kV and 40 mA. The diffraction patterns were recorded using a 0.2 s/0.02° scanning speed from 5° to 60° in 2θ scale. To prevent the atmospheric humidity effect, when necessary the samples were covered during the analysis with a 10 μm polyethylene film.

Preparation of two crystal forms of cAMPNa

Single crystal of solvate cAMPNa·CH$_3$OH·3H$_2$O was grown from methanol aqueous solution. The anhydrous cAMPNa after drying (0.8792 g) was dissolved adequately in 2.1208 g deionized water in a 10 mL tube with a lid under a magnetic stirring condition. The solution was filtered by 0.22 μm filter membrane and was placed in 40 ℃ water bath for 30 min. Then, the preheated methanol (about 4.6 g) was injected quickly to the solution with a stirring for mixing well and held at 40 ℃ for a balance of 2 hours. Subsequently the tube was subjected directly to 25 ℃ for several days (avoiding vibration in whole process; here its supersaturation S=2.79), and crystals would appear and grow. As with the cultivation of methanol trihydrate, another new single crystal of pentahydrate cAMPNa·5H$_2$O can be obtained by controlling crystallization temperature in acetone aqueous solution. Anhydrous cAMPNa powder (0.8792 g) was dissolved in 2.1208 g water initially. After filtration, about 2.35~2.55 g acetone was added in the solution at 40 ℃ and held for 2 hours. Then it was also transferred to 25 ℃ for several days (corresponding S=1.54~1.71 at the initial stage). The layered phenomenon in the solution may be observed initially, yet would disappear with the nucleation and growth of crystals.

The determination of crystal water and methanol

The water content of samples in experiment was determined by Karl Fischer method. Approximately 100 mg of sample was dissolved in methanol and was titrated with a Karl Fischer Reagent (safety pyridine free, AR., Xinzhong Co. Ltd., China) with a titer of 3.8 mg H$_2$O/mL performed in 870 KF Titrino plus (Metrohm, Switzerland) equipped with a 803 Ti stand. Blank titration was necessary before water content determination of sample and each of sample was repeated three times. The methanol content in crystal lattice of sample was determined by gas chromatograph with single point external standard method. Accurate 25.00 mg of sample was dissolved in deionized water to make 5 mL 50 g/L solution. Injection volume was 1 μL and splitless mode was adopted. The experiment was performed using a gas chromatograph (7890A, Agilent, Wilmington, ED, USA) equipped with a flame ionization detector (FID) and an Agilent HP-INNOWAX column (0.25 mm × 60 m). The oven was programmed to heat from 70 to 190 ℃ at a rate of 20 ℃/min, with an initial holding time of 0.5 min and a post holding time of 4 min. The injector and detector temperatures were set to 180 and 220 ℃, respectively. Chromatographic data were recorded and integrated using Agilent data analysis software. The retention time of methanol was 4.0 min.   After the content of water and methanol of sample were determined, it can be converted to corresponding number of water and methanol per cAMP molecule in crystal lattice. The compositions of main samples involved in this study was shown in Table S4.

N$_2$ adsorption isotherm

The N$_2$ sorption experiments of methanol trihydrate that removal of solvent were carried out on a Micromeritics ASAP 2010 CE system at 77 K. Before the experiments, possible solvent on sample powder was removed as much as possible by gradually heating to 110 ℃ from 35 ℃ at a rate of 1 ℃/min, with intermediate steps of 1 h at 80 and 110 ℃ (performed in GDJ-100A high and low temperature alternating incubator, HASUC, China). After pretreatment, the change of sample weight was recorded under the condition of pure N$_2$ at 77 K. The experiments for equilibrium N$_2$ sorption uptake were repeated three times, and the average value was used for comparison. It turned out that no adsorption was observed in the whole process, which indicated that the sample had no detectable pores at this experiment conditions.[1] In fact, the sample present amorphous state when it lost solvent (see Fig. 4d in text).

Table S1. The crystallographic and refinement data for two crystal forms of cAMPNa.

Crystal data		
Formula	cAMPNa·CH$_3$OH·3H$_2$O	cAMPNa·5H$_2$O
Formula Weight	437.29	441.28
Crystal System	orthorhombic	orthorhombic
Space group	P2$_1$2$_1$2$_1$ (No. 19)	P2$_1$2$_1$2$_1$ (No. 19)
a, b, c [Angstrom]	6.5021(10), 7.0943(11), 39.198(6)	6.5585(12), 7.0470(13), 38.869(7)
V [Ang^3]	1808.1(5)	1796.4(6)
Z	4	4
D(calc) [g/cm^3]	1.606	1.632
Mu(MoKa) [/mm]	0.241	0.247
F(000)	912	920
Crystal Size [mm]	0.19 x 0.23 x 0.26	0.22 x 0.24 x 0.26
Data Collection		
Temperature (K)	296	296
Radiation [Angstrom]	MoK$_\alpha$ 0.71073	MoK$_\alpha$ 0.71073
Theta Min-Max [Deg]	2.1, 25.0	1.0, 25.0
Range of *h, k, l*	-7: 7 ; -8: 7 ; -46: 41	-5: 7 ; -8: 8 ; -46: 46
Tot., Uniq. Data, R(int)	10127, 3198, 0.022	12569, 3174, 0.062
Observed data [I > 2.0 sigma(I)]	3029	3059
Refinement*		

Nref, Npar	3198, 256		3174, 254
R, wR2, S	0.0480, 0.1279, 1.16		0.0499, 0.1397, 1.10
Max. and Av. Shift/Error	0.00, 0.00		0.00, 0.00
Flack x	0.1(2)		-0.08(18)
Min. and Max. Resd. Dens. [e/Ang^3]	-0.52, 1.02		-0.43, 0.52
w, where P=(Fo^2^+2Fc^2^)/3	1/[\s^2^(Fo^2^)+(0.0604P)^2^+1.9407P]		1/[\s^2^(Fo^2^)+(0.0757P)^2^+1.6134P]

Note: "*" Refinement of F^2 against all reflections.   The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on all data will be even larger.
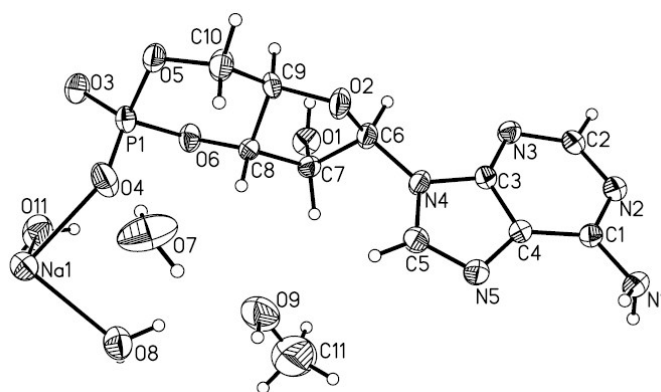

Fig. S1 The molecular ellipsoid diagram of asymmetric cell of cAMPNa methanol trihydrate
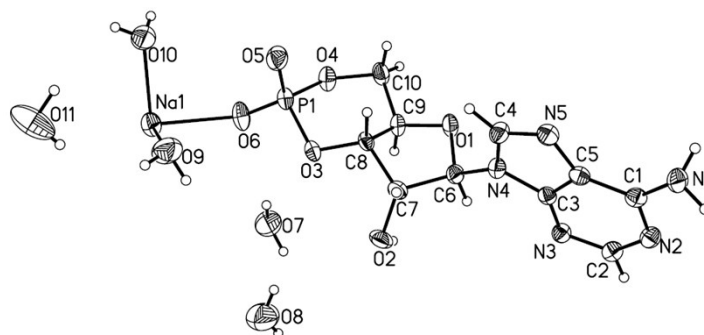

Fig. S2 The molecular ellipsoid diagram of asymmetric cell of cAMPNa pentahydrate
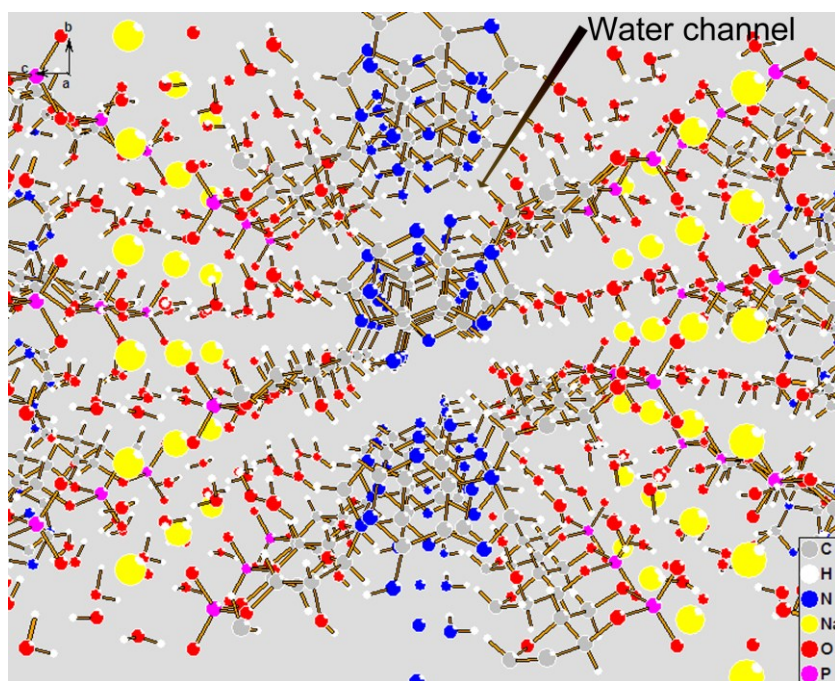
Fig. S3   The molecular packing of pentahydrate and water channels

Table S2. Weight loss in theory vs. removal of water number of two cAMPNa crystal forms

Water loss number Weight loss(%) Crystal forms	1	2	3	4	5
cAMPNa·5H$_2$O	4.08	8.17	12.25	16.33	20.42
cAMPNa·3H$_2$O·CH$_3$OH	12.36 (lose three water molecules only)				
	19.69 (lose three water molecules and one methanol)				

Table S3. The Humidity sensitivity experiment of two crystal forms of cAMPNa

Sample	The weight variation comparing with the original sample (%)	
	After RH 32% conditions for 13 weeks	After RH 76% conditions for 13 weeks
cAMPNa·3H$_2$O·CH$_3$OH	0.11 ± 0.14	0.05 ± 0.12
cAMPNa·5H$_2$O	-0.20 ± 0.21	0.20 ± 0.10

Table S4. The compositions of main samples involved in this study

Sample	Methanol concentration (g/L) *	Mass fraction of methanol in solid, %	Mass fraction of water in solid, %	Methanol number per cAMP in solid	Water number per cAMP in solid
Original composition of two crystal forms					
methanol trihydrate	3.64 ± 0.11	7.28 ± 0.22	12.45 ± 0.41	0.99 ± 0.03	3.02 ± 0.10
pentahydrate	--	--	20.46 ±0.68	--	5.01 ± 0.16
Humidity sensitivity experiment (subjected to corresponding RH conditions for 13 weeks)					
RH 32%- methanol trihydrate	3.64 ± 0.14	7.37 ± 0.28	12.28 ± 0.41	1.01 ± 0.04	2.98 ± 0.11
RH 76%- methanol trihydrate	3.66 ± 0.16	7.29 ± 0.32	12.40 ± 0.37	1.00 ± 0.04	3.01 ± 0.09
RH 32%- pentahydrate	--	--	20.30 ± 0.61	--	4.97 ± 0.15
RH 76%- pentahydrate	--	--	20.51 ± 0.57	--	5.02 ± 0.14
The conversion experiment of solvate (methanol trihydrate) to (pentahydrate) hydrate					
Sampling point ①	3.64 ± 0.11	7.28 ± 0.22	12.45± 0.41	0.99 ± 0.03	3.02 ± 0.10
Sampling point ②	3.39 ± 0.09	6.77 ± 0.18	0.48 ± 0.21	0.80 ± 0.02	0.10 ± 0.04
Sampling point ③	0	0	20.34 ± 0.74	0	4.98 ± 0.18
Dynamic vapor sorption (DVS) experiment of methanol trihydrate					
The initial state	3.64 ± 0.11	7.28 ± 0.22	12.45 ± 0.41	0.99 ± 0.03	3.02 ± 0.10
The end state	0	0	20.26 ± 0.81	0	4.96 ± 0.19

Note: ① original methanol trihydrate crystalline powder; ② after treatment in RH 0% conditions; ③ after treatment in RH 76% conditions. "*" , the methanol concentration referred to corresponding 50 g/L solution of sample according to the assay method mentioned above.
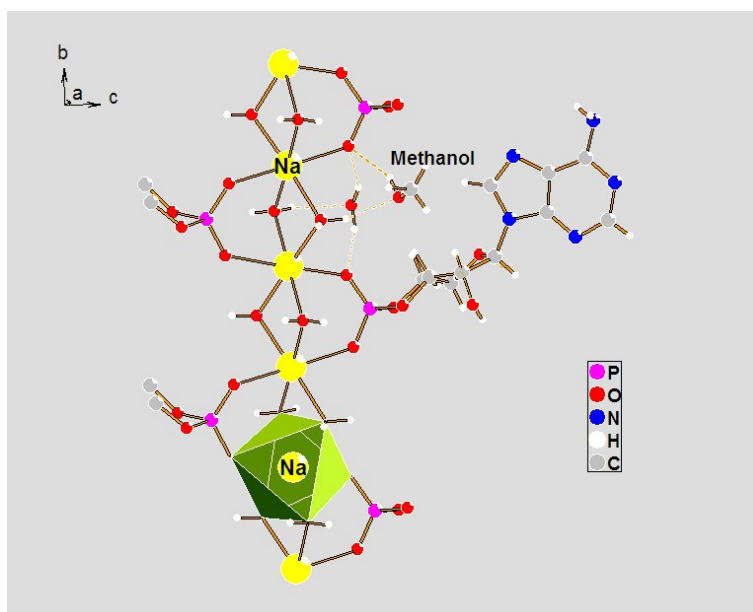
Fig. S4a   Sodium coordination scheme and the location of crystal methanol in cAMPNa methanol trihydrate

Hydrogen bonds are shown as dashed lines. It can be seen that the hydrogen bonding ring are present between crystal solvents and host cAMPNa. The crystal methanol in methanol trihydrate do not take part in metal coordination, whereas its hydroxyl has the ability to form hydrogen bond with surrounding O (crystal water and P-O), see table S4. Sodium ions of methanol trihydrate exhibit octahedrally 6-fold coordination to four water molecules and two O(P-O), with coordination distances varying from 2.37 to 2.48 Å. The case of pentahydrate was similar and shown in Fig. S4b.
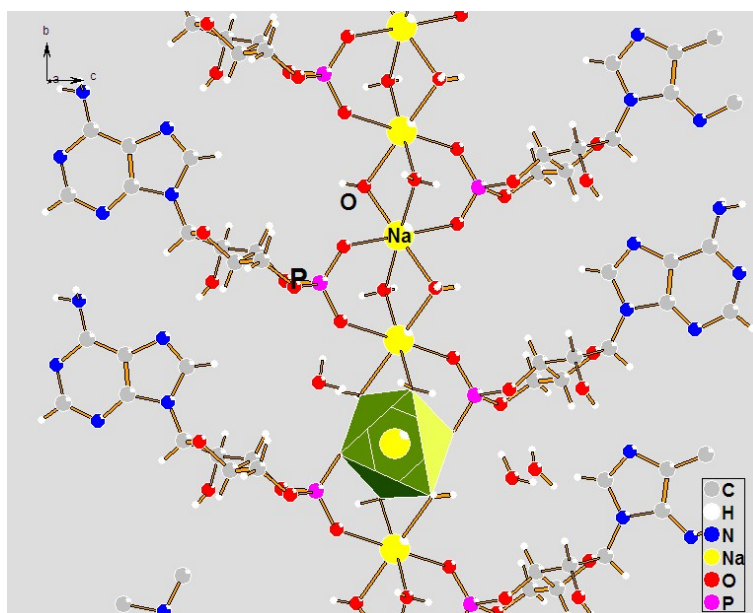

Fig. S4b   The coordination scheme of sodium ions of cAMPNa pentahydrate (present a columnar structure)

Table S5. **The coordination information of sodium ions of two cAMPNa crystal forms**

		Distance (Angstrom)	Object
cAMPNa· CH$_3$OH·3H$_2$O			
Na1	--O4	2.383(3)	(P -O)
Na1	--O8	2.370(3)	crystal water
Na1	--O11	2.483(4)	crystal water
Na1	--O8_a	2.408(3)	crystal water
Na1	--O3_b	2.430(3)	(P -O)
Na1	--O11_b	2.456(4)	crystal water
cAMPNa·5H$_2$O			
Na1	-O9	2.461(5)	crystal water
Na1	-O10	2.368(4)	crystal water
Na1	-O5_a	2.372(4)	(P -O)
Na1	-O6	2.359(3)	(P -O)
Na1	-O9_a	2.483(5)	crystal water
Na1	-O10_a	2.413(4)	crystal water

Table S6. The Hydrogen bond parameters in the cAMPNa methanol trihydrate of methanol molecule to be replaced

D-H..A[*]	D(D-H) / Å	d(H..A) / Å	d(D..A)/ Å	<DHA>
O9-- H9A .. O3	0.8200	2.1700	2.921(5)	152.00
O9 -- H9A .. O6	0.8200	2.5500	3.254(5)	145.00
O8-- H8B .. O9	0.8800	2.0400	2.884(5)	161.00
C8 -- H8 .. O9	0.9800	2.5400	3.323(5)	137.00
[*]D=Donor, A=Acceptor				

Hydrogen bonds with   H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

Table S7. The Hydrogen bond parameters in the cAMPNa pentahydrate of two crystal water molecules replacing the methanol in methanol trihydrate lattice.

D-H..A[*]	D(D-H) / Å	d(H..A) / Å	d(D..A)/ Å	<DHA>
O7-- H7A.. O8	0.8500	2.2100	2.757(6)	122.00
O7-- H7B.. O3	0.8600	2.3300	3.087(5)	146.00
O7-- H7B.. O6	0.8600	2.4200	3.014(4)	127.00
O8-- H8A.. O7	0.8500	2.4100	2.757(6)	105.00
O8-- H8B.. N2	0.8400	2.3400	3.025(5)	139.00
[*]D=Donor, A=Acceptor				

Hydrogen bonds with   H..A < r(A) + 2.000 Angstroms   and   <DHA > 110 deg.

There are five crystal water in the asymmetric unit of cAMPNa pentahydrate, two coordination water bonding with Na ions and three hydrogen water bonding with O(P-O) and N (6-membered pyrimidine ring).

References

1.   J. C. Saint Remi, T. Rémy, H. V. Van, d. P. S. Van, T. Duerinck, M. Maes, V. D. De, E. Gobechiya, C. E. Kirschhock and G. V. Baron, *Chemsuschem*, 2011, **4**, 1074-1077.