Concomitant formation of two different solvates of a hexa-host from a binary mixture of solvents†

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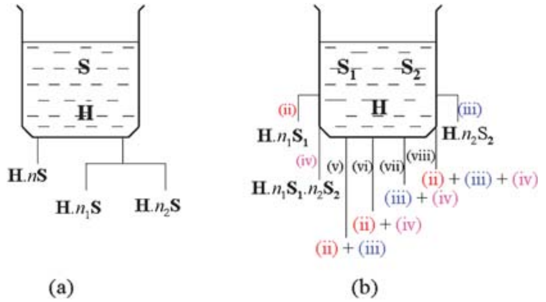
Crystallization of hexakis(4-cyanophenyloxy)benzene from a mixture of two different solvents produces two different solvates concomitantly, which were characterized by X-ray diffraction, thermal analysis and NMR spectroscopy.

Many organic molecules have the intrinsic ability to occlude guest molecules upon crystallization.[1] When the guest molecules are derived from the solvent of crystallization, the resulting inclusion compounds are broadly termed "solvates".[2] Solvates have recently attracted much attention (especially from the pharmaceutical industry) because inclusion of solvent in the crystal lattice can influence properties such as the solubility and dissolution rate of a drug substance.[3] In materials science, solvent inclusion can also affect various properties such as magnetism,[4] ferroelectricity,[5] chemical storage,[6] second harmonic generation[7] and catalysis.[8] Furthermore, selective inclusion of solvent is useful in separation processes.[9]

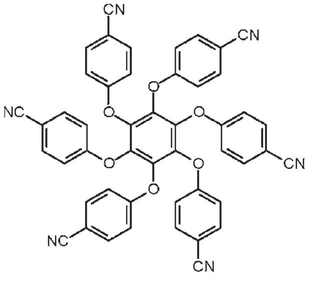
When a host (**H**) is crystallized from a solvent (**S**), either only one kind of solvate (**H**·*n***S**) could be formed, or different solvates such as **H**·n_1**S**, **H**·n_2**S**, *etc.* can result, depending on the stoichiometry of **H** and **S** (Scheme 1a). The solvates of the latter case have been called "concomitant pseudopolymorphs"[10] (we note that the term "pseudopolymorph" in the context of solvates has recently been the subject of some controversy[11]). In principle, there are four possible structural outcomes of crystallizing **H** from a binary mixture of solvents $\mathbf{S_1}$ and $\mathbf{S_2}$: (i) the host can crystallize in its apohost form (*i.e.* without solvent); (ii) **H** can include only solvent $\mathbf{S_1}$ to form $\mathbf{H}\cdot n_1\mathbf{S_1}$; (iii) **H** can include only solvent $\mathbf{S_2}$ to form $\mathbf{H}\cdot n_2\mathbf{S_2}$ and (iv) both solvents can be included to yield a so-called "mixed solvate"[12] $\mathbf{H}\cdot n_1\mathbf{S_1}\cdot n_2\mathbf{S_2}$. Concomitant combinations of (ii) to (iv) yield a further four mixed crystal possibilities (Scheme 1b). While possibilities (ii) to (iv) often occur when an organic host is crystallized from a mixture of solvents,[12] mixed crystal solvates are generally not observed. In a recent report by Nassimbeni *et al.*, it was shown that the solvates obtained by crystallization of a particular host from a binary mixture of solvents depend on the nature and relative proportions of the solvents.[13] Apart from this passing reference to the concomitant occurrence of mixed crystals of solvates, there is, to the best of our knowledge, no other report of this phenomenon. Here we report the rare case of concomitant formation of two different solvates (*i.e.* (ii) + (iii), or (v) in Scheme 1b) of a hexa-host **1** (Scheme 2) from the mixture of methanol (MeOH) and acetonitrile (ACN).



(a) (b)

Scheme 1 Different possibilities of solvate formation.

Compound **1** was prepared and purified according to a previously reported procedure[14] and dissolved in an equal-volume mixture of MeOH and ACN, which was allowed to evaporate slowly at room temperature. After four days, crystals with two different morphologies were observed (Fig. 1). The plate-shaped and needle-shaped crystals were separated manually and both were characterized by X-ray diffraction, thermal analysis and NMR spectroscopy. Single crystal X-ray diffraction (SCD)‡ reveals that the plate-shaped crystals are **1**·MeOH and that the needle-shaped crystals are **1**·ACN (Fig. 2). The MeOH solvate crystallizes in the space group $P\bar{1}$ with one host and one MeOH molecule in the asymmetric unit. The MeOH molecule interacts with **1** by means of O–H···N and C–H···O hydrogen bonds (see ESI†). The ACN solvate crystallizes in the space group *Pbca* with Z = 8 and its asymmetric unit also consists of one host and one



Scheme 2 Hexakis(4-cyanophenyloxy)benzene (**1**).

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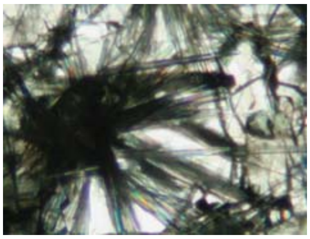
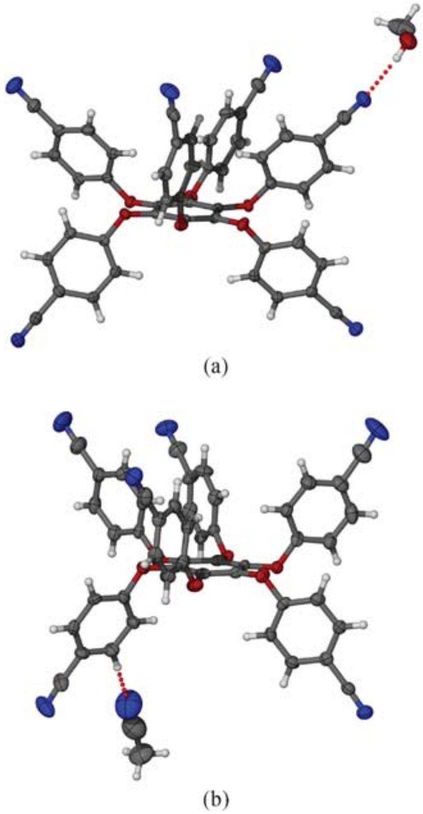


Fig. 1 Photomicrograph of concomitant solvates of **1**.


(a)

(b)

Fig. 2 The asymmetric units of (a) **1**·MeOH and (b) **1**·ACN. Atoms are shown with 70% probability thermal ellipsoids.

guest molecule. The ACN molecules are stabilized by the formation of C–H···N hydrogen bonds with **1**. Packing analysis of **1**·ACN shows that the ACN molecules are also interacting with one another *via* $\pi\cdots\pi$ contacts to form solvent dimers. Interestingly, **1** assumes the *aaabab* conformation in each solvate, which is very unusual for hexa-host molecules.[15,16]

Thermal analysis of both the solvates was carried out and the results are shown in Fig. 3. The TGA traces of both solvates indicate that solvent loss occurs as a single-step process in each case. The DSC thermogram of **1**·MeOH (Fig. 3a) exhibits a small endotherm at T_{on} = 120 °C (T_{on} is the onset temperature), representing loss of methanol, followed by melting of **1** at T_{on} = 270 °C. Similarly, the DSC thermogram of **1**·ACN (Fig. 3b) shows an endotherm at T_{on} = 171 °C associated with the loss of acetonitrile, followed by melting at T_{on} = 270 °C. The parameter $T_{\text{on}} - T_{\text{b}}$ can be used as a reliable measure of the thermal stability of the solvates

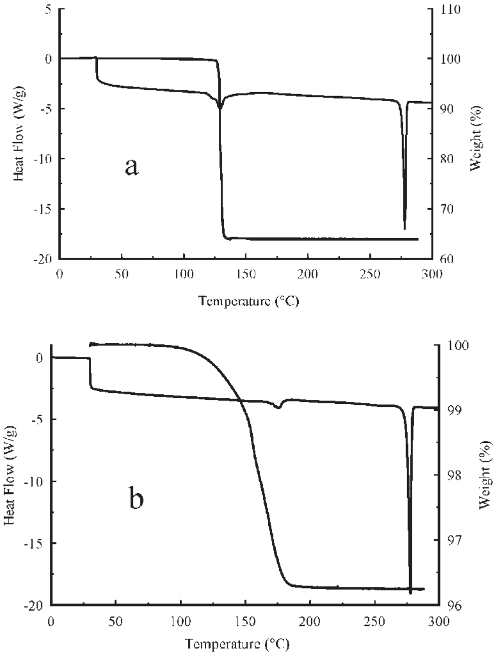


Fig. 3 TGA and DSC thermograms of (a) **1**·MeOH and (b) **1**·ACN.

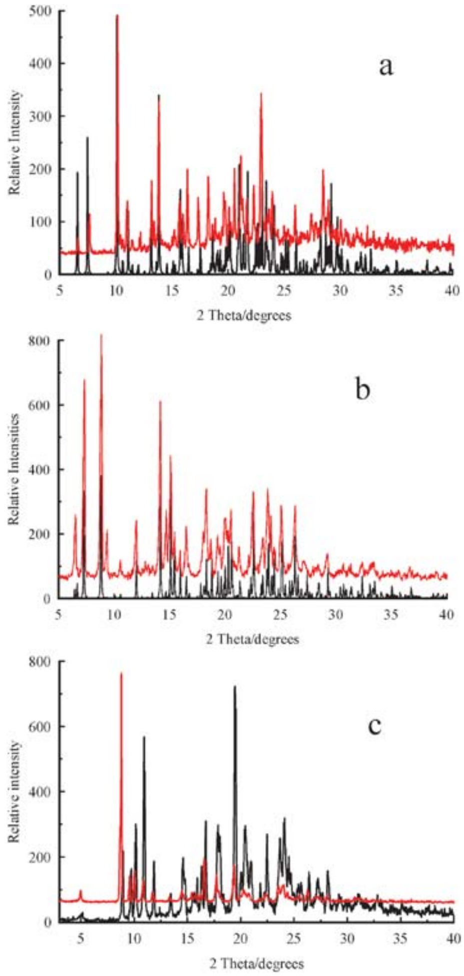


Fig. 4 Overlay of experimental (red) and simulated (black) XRPD patterns of (a) **1**·MeOH and (b) **1**·ACN. (c) Experimental XRPD patterns of desolvated **1**·MeOH (black) and **1**·ACN (red).

where T_b is the boiling point of the solvent.[17] For **1**·MeOH $T_{on} - T_b = 56$ °C and for **1**·ACN it is 89 °C. These parameters suggest that the acetonitrile solvate is more thermally stable than the methanol solvate, although the latter contains stronger hydrogen bonds between host and guest.

The manually separated crystals were ground mildly using a mortar and pestle and the powdered samples were analyzed by X-ray powder diffraction (XRPD) in order to reveal the bulk phase identities of the plate- and needle-shaped crystals. The experimental XRPD patterns were compared with the simulated patterns from the SCD structures. Fig. 4 shows excellent agreement between experimental and simulated patterns for the two solvates. The **1**·MeOH and **1**·ACN solvates were also prepared separately by dissolving **1** in the corresponding solvent in each case. The XRPD patterns of the separately prepared solvates are similar to those of the concomitant solvates. Desolvation of both solvates by heating at 200 °C yields the same crystalline phase of **1** as confirmed by XRPD (Fig. 4c).

The separated concomitant solvates were analyzed by NMR spectroscopy for further confirmation of different solvent inclusion by **1**. ^{13}C NMR spectra show the characteristic peaks of the methyl carbon atoms of methanol and acetonitrile at 49.3 ppm and 1.87 ppm, respectively (see ESI†). The cyano carbon atom of acetonitrile is confirmed by a peak at 118.7 ppm. The NMR results strongly suggest that the crystals of the two different morphologies include methanol and acetonitrile separately.

In summary, we have highlighted the rare occurrence of the formation of two different solvates concomitantly from a binary mixture of solvents. We have demonstrated this phenomenon using a hexa-host system crystallized from a mixture of methanol and acetonitrile, and our results are supported unequivocally by single-crystal X-ray diffraction, powder X-ray diffraction, thermal analysis and NMR spectroscopy.

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Notes and references

‡ Crystal data for **1**·MeOH: $C_{49}H_{28}N_6O_7$, $M = 812.77$, colorless plate, $0.35 \times 0.31 \times 0.22$ mm^3, triclinic, space group $P\bar{1}$ (No. 2), $a = 9.5852(7)$, $b = 14.1037(10)$, $c = 15.5025(11)$ Å, $\alpha = 72.741(1)$, $\beta = 84.113(1)$, $\gamma = 85.594(1)°$, $V = 1988.4(2)$ Å^3, $Z = 2$, $D_c = 1.357$ g cm^{-3}, $F_{000} = 840$, CCD area detector, MoK$_\alpha$ radiation, $\lambda = 0.71073$ Å, $T = 100(2)$ K, $2\theta_{max} = 56.7°$, 23372 reflections collected, 9236 unique ($R_{int} = 0.0476$). Final GooF = 1.037, $R_1 = 0.0551$, w$R_2 = 0.1146$, R indices based on 6218 reflections with $I > 2\sigma(I)$ (refinement on F^2), 561 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.093$ mm^{-1}.
Crystal data for **1**·ACN: $C_{50}H_{27}N_7O_6$, $M = 821.79$, colorless thin needle, $0.23 \times 0.11 \times 0.05$ mm^3, orthorhombic, space group $Pbca$ (No. 61), $a = 26.101(7)$, $b = 11.662(3)$, $c = 27.000(7)$ Å, $V = 8218(4)$ Å^3, $Z = 8$, $D_c = 1.328$ g cm^{-3}, $F_{000} = 3392$, CCD area detector, MoK$_\alpha$ radiation, $\lambda = 0.71073$ Å, $T = 100(2)$ K, $2\theta_{max} = 50.1°$, 33775 reflections collected, 7245 unique ($R_{int} = 0.1423$). Final GooF = 1.018, $R_1 = 0.0789$, w$R_2 = 0.1669$, R indices based on 4146 reflections with $I > 2\sigma(I)$ (refinement on F^2), 569 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.090$ mm^{-1}.

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