Cholanamide components for organic alloys; expanding the scope of nanoporous steroidal ureas†

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Amide-linked side-chains can substitute for esters in crystalline nanoporous steroidal ureas (NSPUs). This efficient conjugation method increases the versatility of NPSUs, and should aid the inclusion of complex functional units in the crystal channels.

The rational design of porous solids is a major goal of crystal engineering.[1] Crystalline systems which contain pores ranging from ~0.5 to 2.0 nm are of particular interest, as this can allow penetration by a range of molecular guests. Such absorptive properties can lead to applications including gas storage,[2] catalysis[3] or molecular separations.[4] There is thus much interest in the preparation of nanoporous crystals, especially where properties can be tailored for different purposes. Success has been achieved using various approaches, including metal–organic frameworks, preformed molecular cavities ("intrinsically porous" molecules[5]) and covalent organic frameworks.[1e,2a,f,6] However, the creation of pores through the crystallisation of non-macrocyclic organic molecules ("extrinsic porosity") remains a particular challenge. There are especially few examples where pore size and material properties can be tuned,[7] and even in those cases the possible variations within the packing motif are relatively narrow.

We have recently described a family of extrinsically porous crystals, the "nanoporous steroidal ureas" (NPSUs), which provides exceptional scope for variation.[8] The crystals are formed from esters of substituted cholanoic acids, and the variations are possible (in part) because the ester group can be changed without affecting the packing (see below). Herein we report that the corresponding cholanamides may also be incorporated in NPSU crystals. This discovery expands the range of potential NPSUs, with particular relevance to the inclusion of complex functional units in the crystal pores.

An overview of the NPSU crystal family is given in Fig. 1. The molecules which form the crystals are represented by the general formula **1** (Fig. 1a) and are accessible in as little as 5 steps from cholic acid **2**.[9] The crystal structure of prototype **1a**[8a] is shown in Fig. 1b, viewed down the *c* axis. The packing involves the formation of helices with hexagonal symmetry (space group = $P6_1$) surrounding solvent-filled channels. The terminal units (NHPh and OMe in this case) lie at the surface of these channels, largely constituting the walls. The channels are unusually wide (~1.6 nm average diameter for **1a**), so there is room for these groups to expand without disturbing the $P6_1$ crystal packing. Accordingly, groups R^1 and R^2 can be varied to give a range of isostructural crystals with different channel diameters and surface characteristics.[8b,e] Moreover, because their structures are so similar, different variants can co-crystallise in continuously variable ratios to form "organic alloys" (Fig. 1c).[8c,d] This facilitates tuning, and also allows very large units to be placed in the channels (through conjugation with the steroid then "doping" in a matrix of simpler "host" NPSU molecules). Studies on **1a** have confirmed that it possesses permanent porosity (as indicated by evacuation and gas adsorption), and that it can take up a range of organic molecules including the C_{30} hydrocarbon squalene.[8e]

Although new NPSUs may be created by changing both R^1 and R^2, the latter has practical advantages. The methyl ester **1a** is especially easy to synthesise,[9] and modifying the methoxy group requires just hydrolysis and re-esterification. However while this process is often straightforward, esterification can be problematic especially if the alcohol is complex, hindered and/or hydrophilic. Amide formation is a highly reliable method of conjugation, and many groups of interest (*e.g.* peptides) are available as amines. Thus incorporation of cholanamides **3** would enhance the potential of NPSUs as functional materials. We therefore decided to establish whether the NPSU motif could be extended to cholanamides, at least for simple test cases.

The ability of amides **3** to participate in NPSU structures could be compromised by steric hindrance in the case of tertiary

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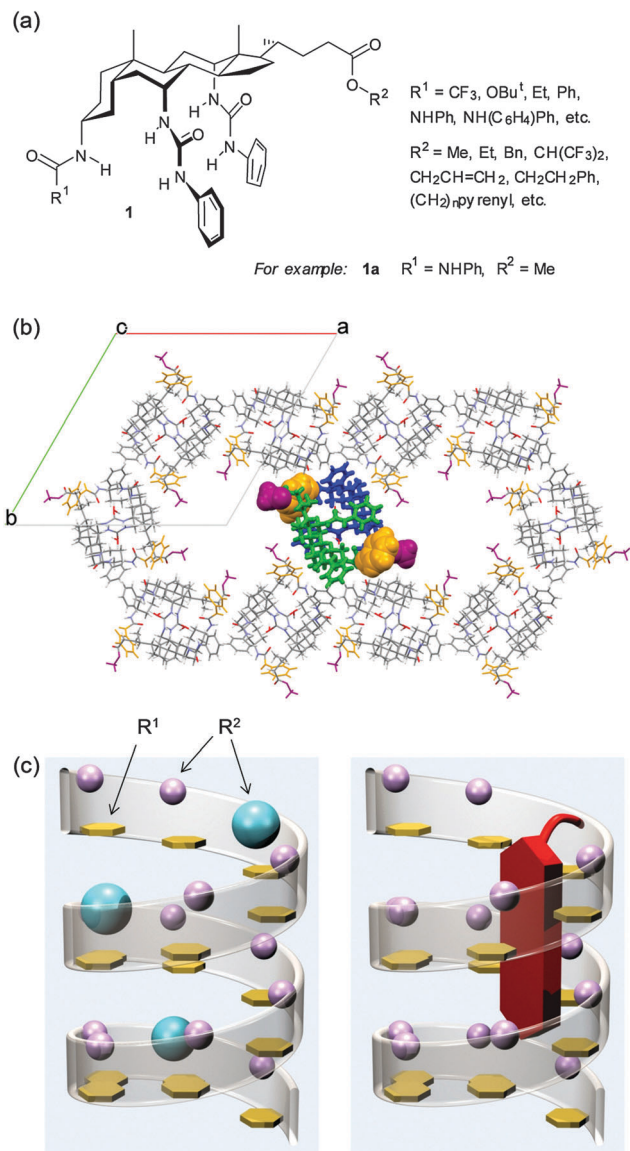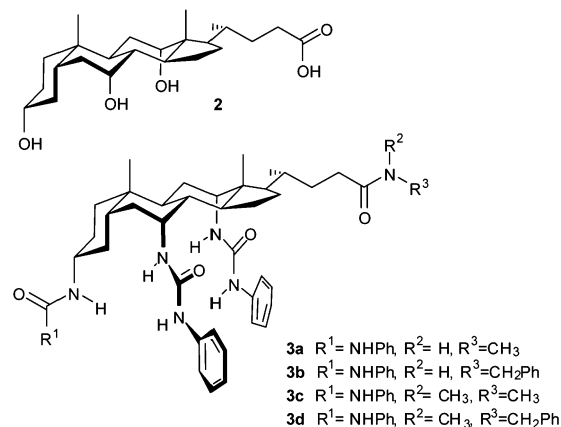
Fig. 1 The NPSU crystal family. (a) General structure of NPSU monomers. (b) NPSU **1a** in the crystal, viewed down the *c* axis. Terminal groups R^1 (NHPh) and OR^2 (OMe) are coloured gold and magenta respectively. To show the positioning of the individual molecules, two are highlighted (green and blue) with terminal groups in space filling mode. (c) Schematic depictions of channels in crystals, showing the helical arrangements of R^1 and R^2. Left: a solid solution with two types of R^2. Right: placing a bulky R^2 in the channel through low-level doping.

amides, or by the potential for new NH···X hydrogen bonds in the case of secondary amides. We chose to study examples of both types, the secondary amides **3a,b** and the tertiary amides **3c,d**. Amides **3a–d** were prepared from tris-urea **1a** by ester hydrolysis followed by coupling to methylamine, benzylamine, *N*-methylbenzylamine and dimethylamine using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) as condensing agent.

Attempts were made to crystallise **3a–d** using our standard method for NPSUs, *i.e.* dissolving in acetone or methyl acetate, adding water, and allowing the organic solvent to evaporate. Unfortunately these trials were unsuccessful, yielding only white amorphous solids. Attempted crystallisations from other solvents (*e.g.* methanol, ethanol) produced similar results.

3a R^1= NHPh, R^2= H, R^3=CH$_3$
3b R^1= NHPh, R^2= H, R^3=CH$_2$Ph
3c R^1= NHPh, R^2= CH$_3$, R^3=CH$_3$
3d R^1= NHPh, R^2= CH$_3$, R^3=CH$_2$Ph

While amides **3a–d** might not crystallise as pure compounds, this did not preclude their incorporation in NPSUs. Given that NPSUs can form alloys,[8c] it seemed likely that crystals of an ester such as **1a** might accept the amides as substitutes or dopants. Accordingly, we prepared mixtures of **3a–d** with ester **1a** in the ratios **1a**:**3** = 1:1, 2:1, and 5:1, dissolved in acetone, and subjected them to the standard NPSU crystallisation method (see above). All the 1:1 mixtures failed to give crystals, yielding only amorphous solids. The same was true of the 2:1 mixtures incorporating secondary amides **3a** and **3b**. However, the mixtures **1a**:**3c,d** = 2:1, and all 5:1 mixtures, gave needle-like crystals similar in appearance to those given by **1a** (see Table 1). The collected crystals were all analyzed by ^{1}H NMR spectroscopy to give the bulk compositions shown in Table 1, while the presence of both the components within individual crystals was confirmed by ESI-MS on single crystals. Attempts were made to detect the amide components in the **1a·3b–d** mixtures using single crystal X-ray diffraction (SCXRD).[10] However, while the data yielded evidence of the second components, it was not possible to model the amide substituents. The crystallography did provide confirmation that the crystals were indeed NPSUs, with the $P6_1$ packing and cell parameters listed in Table 1.

Although we cannot be certain that the distribution of **1a** and **3** is random within the crystals, these results point clearly to co-crystallisation and, most probably, the formation of solid solutions (organic alloys). In particular, the ESI-MS spectra on single crystals show that **1a** and **3** occur together, while the

Table 1 Solid solutions formed by steroidal ureas **3** and **1a**

Components	Initial ratio	Ratio in crystals (bulk)[a]	Crystallographic unit cell details[b]		
			a,b [Å]	c [Å]	V [Å^3]
1a, 3a	5:1	83:17	[c]	[c]	[c]
1a, 3b	5:1	76:24	29.0457(8)	11.4742(3)	8383.3(4)
1a, 3c	2:1	83:17	29.0994(4)	11.4992(3)	8432.7(3)
1a, 3c	5:1	91:9	29.0759(4)	11.4900(3)	8441.4(3)
1a, 3d	2:1	70:30	29.0240(7)	11.4753(3)	8371.6(4)
1a, 3d	5:1	83:17	29.1007(3)	11.4979(2)	8432.5(2)

[a] Determined by ^{1}H NMR integration. [b] Standard deviations are given in parentheses. [c] Not determined.

inability of **3** to crystallise alone suggests that all-amide domains are unlikely. It is encouraging to find that all the amides were incorporated, but interesting to note the difference between the secondary and tertiary amides. In the former case, alloy formation was only possible for the most dilute mixture (**1a**:**3a,b** = 5:1). However, when it did occur incorporation was efficient, the ratio in the crystals being similar to that in solution. For the tertiary amides incorporation was possible at higher starting concentrations, but was slightly less efficient (especially in the case of **3c**).

In conclusion, we have found that the cholanoate NPSUs **1**, already capable of variation and alloy formation, can be further modified by inclusion of cholanamides **3**. If this discovery can be generalised it opens the way to a range of new materials in which complex functional units are positioned in the channels of nanoporous crystals.

Notes and references

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