

## Cocrystallization of adamantane-1,3-dicarboxylic acid and 4,4'-bipyridine

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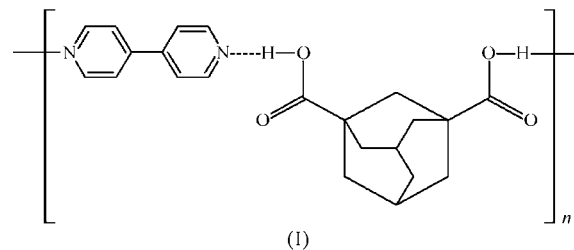
The cocrystallization of adamantane-1,3-dicarboxylic acid (adc) and 4,4'-bipyridine (4,4'-bpy) yields a unique 1:1 cocrystal,  $C_{12}H_{16}O_4 \cdot C_{10}H_8N_2$ , in the  $C2/c$  space group, with half of each molecule in the asymmetric unit. The mid-point of the central C—C bond of the 4,4'-bpy molecule rests on a center of inversion, while the adc molecule straddles a twofold rotation axis that passes through two of the adamantyl C atoms. The constituents of this cocrystal are joined by hydrogen bonds, the stronger of which are O—H...N hydrogen bonds [ $O \cdots N = 2.6801(17) \text{ \AA}$ ] and the weaker of which are C—H...O hydrogen bonds [ $C \cdots O = 3.367(2) \text{ \AA}$ ]. Alternate adc and 4,4'-bpy molecules engage in these hydrogen bonds to form zigzag chains. In turn, these chains are linked through  $\pi$ – $\pi$  interactions along the  $c$  axis to generate two-dimensional layers. These layers are neatly packed into a stable crystalline three-dimensional form *via* weak C—H...O hydrogen bonds [ $C \cdots O = 3.2744(19) \text{ \AA}$ ] and van der Waals attractions.

## Comment

As awareness of the importance of pharmaceutical cocrystallization grows, it becomes imperative to fully understand and investigate the intermolecular relationships in a cocrystal. Cocrystals are, by definition, a crystalline material that consists of different molecular species held together by noncovalent forces (Aakeröy, 1997). Cocrystallization may change the physical properties of active pharmaceutical ingredients (APIs), including their stability, hygroscopicity, dissolution rate, solubility and bioavailability (Thayer, 2007). It may be possible to use cocrystallization to solve the problem that most pharmaceutical developers are now facing: the most stable crystalline forms of drugs are, often, the most insoluble ones. Moreover, some expensive drugs are not optimally absorbed into the bloodstream, an economically unfavorable situation. A great way to circumvent this problem is to combine an API with an API-former, a molecule that weakly bonds with the API, usually *via* a pyridine or amine group

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(Thayer, 2007). The cocrystal formed will very likely exhibit solubility similar to that of an amorphous phase while also retaining the stability of crystalline salts. For example, the insoluble drug itraconazole is actually very stable and quite soluble as a cocrystal with various 1,4-dicarboxylic acids (Remenar *et al.*, 2003).



The title cocrystal, (I), is formed by adamantane-1,3-dicarboxylic acid (adc) with 4,4'-bipyridine (4,4'-bpy). Because adc contains the carboxyl functional group prevalent among APIs, it is possible to delve further into the complexity of pharmaceutical cocrystals through analysis of intermolecular relationships in this particular cocrystal. The dicarboxylic acid adc has been explored previously as a component of cocrystals with several different pyridine ligands, such as 1,2-di-4-pyridylethylene (dipy-ete) and 1,2-di-4-pyridylethane (Zeng *et al.*, 2006). The rigid base 4,4'-bpy was chosen as the cocrystal former in the present study because it readily participates in hydrogen bonds with organic molecules with attached carboxyl groups (Du *et al.*, 2005); it is also a weak bidentate base commonly used in crystal engineering on account of its bridging abilities (Cowan *et al.*, 2001).

There are several types of packing interactions in (I). The most dominant is the O—H...N hydrogen bond formed between a carboxyl group and a pyridine N atom. The length of this hydrogen bond [ $O \cdots N = 2.6801(17) \text{ \AA}$ ] is very close to those of O—H...N bonds found in similar cocrystals [2.6323(15)  $\text{ \AA}$  in the adduct of 2,5-dihydroxy-1,4-benzoquinone and 4,4'-bpy (Cowan *et al.*, 2001), and 2.625(2)  $\text{ \AA}$  in 4,4'-bpy-*N,N'*-dioxide-3-hydroxy-2-naphthoic acid (1/2) (Lou & Huang, 2007)]. The refined position of the carboxyl H atom clearly shows that the acid retains the H atom rather than transferring it to the adjoining pyridine N atom (Fig. 1). Because the adc molecule is V-shaped with two flexible carboxyl arms, a series of interchanging adc and 4,4'-bpy

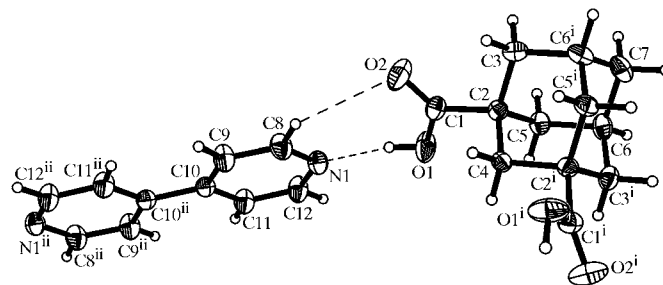


Figure 1

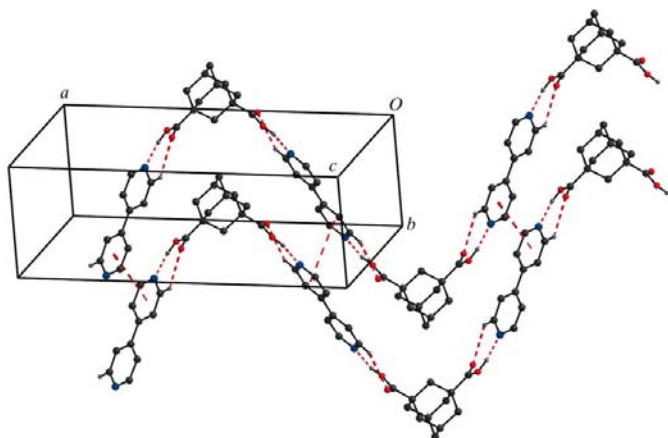
A plot of the title compound, shown with 30% probability displacement ellipsoids. Hydrogen bonds are shown as dashed lines. [Symmetry codes: (i)  $-x, y, -z + \frac{1}{2}$ ; (ii)  $-x + \frac{1}{2}, -y + \frac{5}{2}, -z + 1$ .]

molecules results in a zigzag chain, thus forming a one-dimensional structure (Fig. 2). To comply with the general packing pattern, the angle of the hydrogen bond formed between the adc and 4,4'-bpy molecules is  $168 (2)^\circ$ .

In addition to the strong O—H...N hydrogen bond, a weaker C—H...O hydrogen bond also exists between the adc and 4,4'-bpy molecules (C8—H8...O2). The length of this bond [C...O =  $3.367 (2) \text{ \AA}$ ] is comparable to those of most C—H...O hydrogen bonds found in crystals with similar structures, for example, the adduct of 2,5-dihydroxy-1,4-benzoquinone and 4,4'-bpy [C...O =  $3.2082 (17) \text{ \AA}$ ; Cowan *et al.*, 2001]. The combination of these two hydrogen bonds between the adc and 4,4'-bpy molecules is denoted as  $R_2^2(7)$  using graph-set notation (Bernstein *et al.*, 1995).

Because 4,4'-bpy is characterized by two aromatic rings, electrostatic forces of attraction occur between face-to-face rings (Lou & Huang, 2007). Thus,  $\pi$ - $\pi$  stacking is established between infinite stacks of 4,4'-bpy molecules along the *c* axis. Although each 4,4'-bpy molecule is parallel to an adjacent one, the position of each is shifted so that one is not directly over the other. The perpendicular distance between two parallel molecules is  $3.46 \text{ \AA}$ . This weak interaction holds the hydrogen-bonded chains together, supporting a two-dimensional framework. Similar  $\pi$ - $\pi$  interactions between interlocking chains also control the crystal packing of the adc-dipy-ete cocrystal (Zeng *et al.*, 2006). In addition, one C—H bond of the pyridyl ring is involved in a C—H...O interaction (C11—H11...O1) with the carboxyl group of the adc molecule at  $(-x + \frac{1}{2}, y + \frac{1}{2}, -z + \frac{1}{2})$ . These weak hydrogen bonds further join the two-dimensional layers into a three-dimensional network.

Thermogravimetric analysis (TGA) confirms that adc and 4,4'-bpy are in a 1:1 ratio in the cocrystal. According to the molar weights of adc and 4,4'-bpy, the mass of adc to that of 4,4'-bpy should be 1.44. The TGA results show that the first weight loss is caused by the departure of 4,4'-bpy from the crystal, starting at around 398 K, which accounts for about 41% of the total mass. It is then followed by a mass loss of about 59% representing loss of adc, beginning at about 453 K. This test gives rise to an adc-to-bpy mass ratio of 1.43.



**Figure 2**

Zigzag chains of adc and 4,4'-bpy along the *a* axis. Hydrogen bonds and  $\pi$ - $\pi$  interactions are shown as dashed lines.

## Experimental

Adamantane-1,3-dicarboxylic acid (3 mmol, 67.4 mg) was mixed with 4,4'-bipyridine (3 mmol, 46.8 mg) in a 1:1 stoichiometry and immersed in an aqueous solution (10 ml). The resulting mixture was placed in a Teflon-lined stainless steel vessel, which was heated to 424 K for 2 d. Two types of colorless crystals were engendered, *viz.* the desired cocrystal, which is block-like, mixed with unreacted sheet-like crystals of adc.

### Crystal data

$C_{12}H_{16}O_4 \cdot C_{10}H_8N_2$	$V = 1894.5 (2) \text{ \AA}^3$
$M_r = 380.43$	$Z = 4$
Monoclinic, $C2/c$	Mo $K\alpha$ radiation
$a = 21.5610 (16) \text{ \AA}$	$\mu = 0.09 \text{ mm}^{-1}$
$b = 7.2378 (5) \text{ \AA}$	$T = 295 (2) \text{ K}$
$c = 12.1520 (9) \text{ \AA}$	$0.38 \times 0.31 \times 0.22 \text{ mm}$
$\beta = 92.580 (1)^\circ$	

### Data collection

Bruker SMART CCD area-detector diffractometer	9381 measured reflections
Absorption correction: multi-scan (SADABS; Bruker, 2001)	2360 independent reflections
$T_{\min} = 0.966, T_{\max} = 0.980$	2005 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.021$

### Refinement

$R[F^2 > 2\sigma(F^2)] = 0.048$	176 parameters
$wR(F^2) = 0.121$	All H-atom parameters refined
$S = 1.00$	$\Delta\rho_{\max} = 0.27 \text{ e \AA}^{-3}$
2360 reflections	$\Delta\rho_{\min} = -0.23 \text{ e \AA}^{-3}$

**Table 1**

Hydrogen-bond geometry ( $\text{\AA}, ^\circ$ ).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
O1—H1...N1	0.90 (3)	1.80 (3)	2.6801 (17)	168 (2)
C11—H11...O1 <sup>iii</sup>	0.946 (19)	2.576 (19)	3.2744 (19)	130.9 (15)
C8—H8...O2	0.964 (19)	2.67 (2)	3.367 (2)	129.6 (14)

Symmetry code: (iii)  $-x + \frac{1}{2}, y + \frac{1}{2}, -z + \frac{1}{2}$ .

All H atoms were found in intermediate difference Fourier maps and were refined fully with isotropic displacement parameters [ $C-H = 0.94 (2)$ – $1.019 (18) \text{ \AA}$ ].

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2001); software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ3107). Services for accessing these data are described at the back of the journal.

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