Supplementary Material (ESI) for Chemical Communications
This journal is (C) The Royal Society of Chemistry 2006

Development of a Pharmaceutical Cocrystal of a Monophosphate Salt with Phosphoric Acid

Alex M. Chen,*[a] Martha E. Ellison,*[a] Andrey Peresypkin, [a] Robert M. Wenslow, [a] Narayan Variankaval, [a] Cecile G. Savarin, [a] Theresa K. Natishan, [a] David J. Mathre, [a] Peter G. Dormer, [a] Danielle H. Euler, [b] Richard G. Ball, [a] Zhixiong Ye, [a] Yaling Wang [a] and Ivan Santos [a]

1. Crystallographic Data

Compound $C_{34}H_{53}ClF_2N_4O_{10}P_2$, M_r = 813.190, monoclinic, $P2_1$, a = 8.901(5), b = 10.995(6), c = 21.876(12) Å, β=100.157(9)°, V = 2107.3(19) Å^3, Z = 2, D_x = 1.282 gcm^{-3}, monochromatized radiation λ(Mo) = 0.71073 Å, μ = 0.23 mm^{-1}, $F(000)$ = 860, T = 298° K. Data were collected on a Bruker CCD diffractometer to a θ limit of 26.46° which yielded 20016 reflections. There are 8502 unique reflections with 6714 observed at the 2σ level ; R(int) = 0.050. The structure was solved by direct methods (SHELXS-97, Sheldrick, G.M. *Acta Crystallogr.*, 1990, A46, 467-473) and refined using full-matrix least-squares on F^2 (SHELXL-97, Sheldrick, G.M. *SHELXL-97. Program for the Refinement of Crystal Structures.* Univ. of Göttingen, Germany). The data were corrected for absorption, and other effects, using the SADABS program (Sheldrick, G.M. (1996) *SADABS.* University of Göttingen, Germany). The final model was refined using 491 parameters and all 8502 data. All non-hydrogen atoms were refined with anisotropic thermal displacements. The final agreement statistics are: R = 0.098 (based on 6714 reflections with $I > 2\sigma(I)$), wR = 0.224, S = 1.18 with $(\Delta/\sigma)_{max}$ = 0.01. The crystals available for analysis were of moderate quality and this presented some problems during the refinement process; in the final model there are a number of atoms, in particular F2, C6, O53 and O54 with highly irregular ADP values. The maximum peak height in a final difference Fourier map is 1.009 eÅ^{-3}, is not located near any other atom (the closest approach is 2.6 Å to H30C), and is without chemical significance.

In the present structure the P51-based phosphate has two longer P-O distances and two shorter ones. The two shorter distances, 1.475(9) and 1.461(9) are not significantly different from each other (only 1.1 sigma), but they are significantly shorter than the two longer distances. It is also noted that O53 and O54 have large and highly anisotropic ADP values thus making it even more difficult to decide what the true bond distance is to P51 for these two O atoms. Accepting that the double-bonded O will appear as a shorter bond then it is probable that either P51-O53 or P51-O54 is the double-bonded O with the other being a hydroxyl. Since the bond distances alone are insufficient to absolutely determine the bond orders, we examined the interatomic distances to see if a self-consistent model for hydroxyl assignment could be derived for the O atoms of the two phosphate groups. For the P41-based phosphate: O41 has a quite short distance to N1 so we have assigned a delta negative charge to it and propose it to be tightly coupled to the delta positive charge on the protonated N1 atom. The O42, O43 and O44 atoms have interatomic distances appropriate for H-bonding; one of these atoms is presumably the phosphoryl oxygen with the others being two hydroxyls. Since O42 has only one short contact (2.610 Å to O1 of the organic moiety) it is safely assigned as a hydroxyl. The two P-O distances for O43 and O44 differ by slightly more that three sigma so we'll take the shorter distance to be associated with at least a partial double bond thereby making O44 the phosphoryl oxygen.

In determining the hydroxyl assignment in the second phosphate we rely on the already established assignment of the hydroxyls in the P41 phosphate. O51 has a short contact to O41 (the O bearing the delta negative charge) so O51 must be a hydroxyl. O52 has one short contact to O2 (carbonyl) of the organic moiety so O52 is a hydroxyl. O53 has a short contact to O44 of the other phosphate and we have already assigned O44 as the phosphoryl oxygen; that makes O53 a hydroxyl. O54 has a short contact to O43 and since O43 is a hydroxyl this requires that O54 be the phosphoryl oxygen. Although an equally self-consistent assignment could be made assuming O43 and O53 are the phosphoryl oxygens we feel that given the moderate quality of this structure determination, which precludes deciding between the two models based on bond distances, our arguments above slightly favor the choice we have presented.

CCDC 619263 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2.

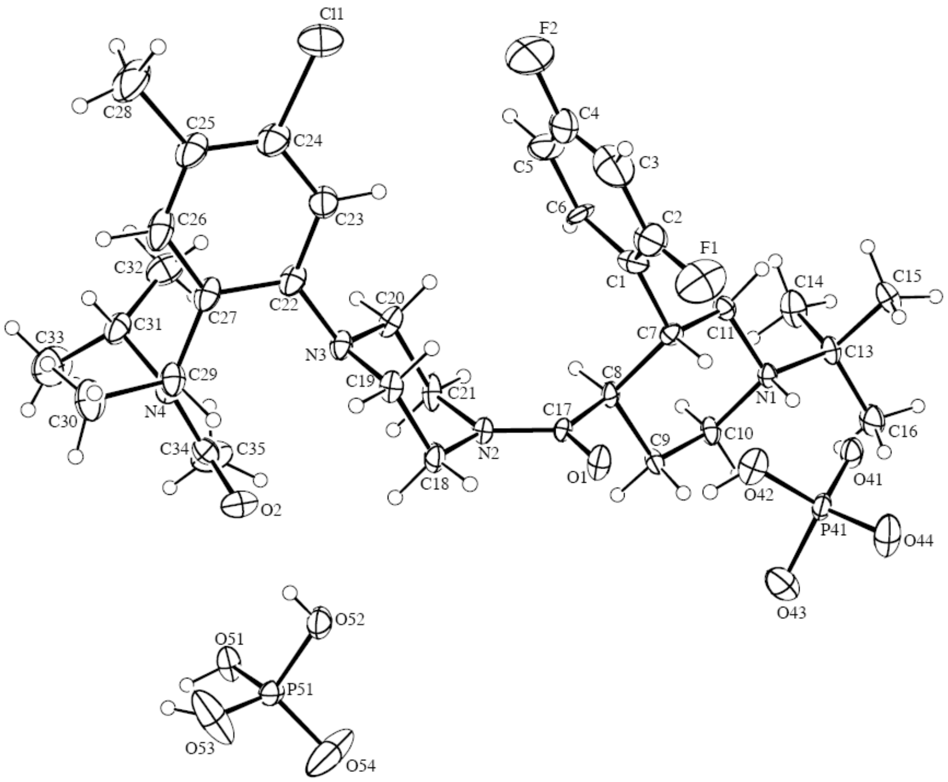


Figure S1. ORTEP representation of the structure model with the atom numbering scheme. The non-H atoms are drawn with thermal ellipsoids at the 20% level while the H atoms are drawn at an arbitrary size.

3. Helix structure of the hydrogen-bonded phosphoric acid units

Crystallographically inequivalent phosphoric acid molecules in the unit cell are hydrogen-bonded to each other in neighboring unit cells. Figure S2 shows the structure of the cocrystal of compound I monophosphate salt with phosphoric acid.

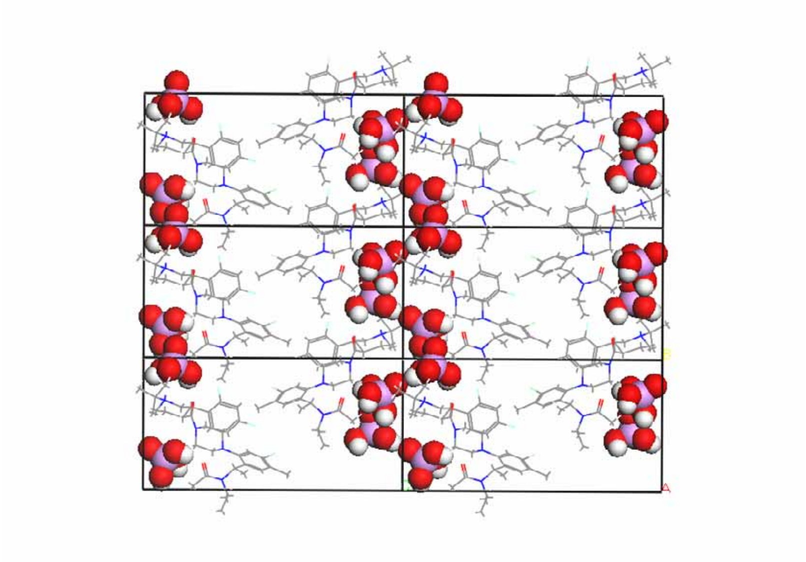


Figure S2. Crystal structure of cocrystal of Compound I monophosphate salt with phosphoric acid

The same structure viewed down the b-axis is shown in Figure S3(a). Figure S3(b) shows the same lattice with only the phosphoric acid molecules.

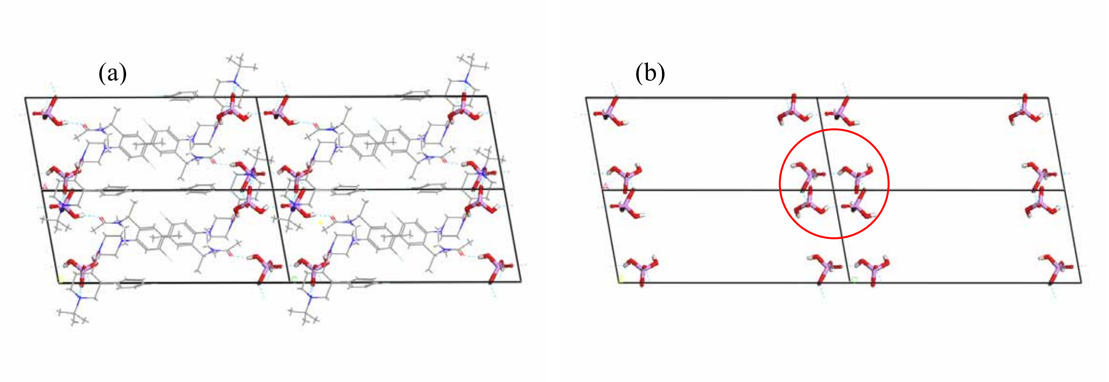
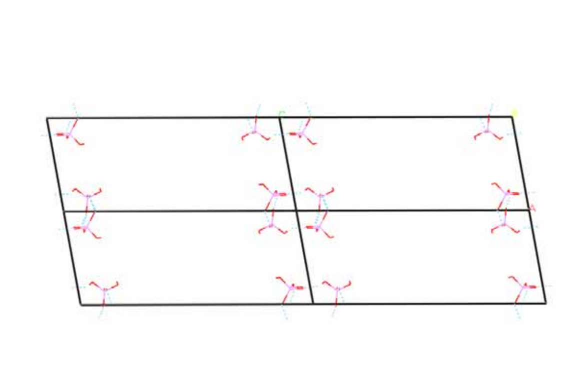

(a)
(b)

Figure S3. (a) Four unit cells of the cocrystal. (b) Viewed down b-axis with API molecules removed.

Figure S4 shows the helical nature of the hydrogen-bonded phosphoric acid molecules viewed head-on the b-axis. The components of the hydrogen-bonded chain alternate between four different unit cells which is apparent from Figures S3(b) and S4.



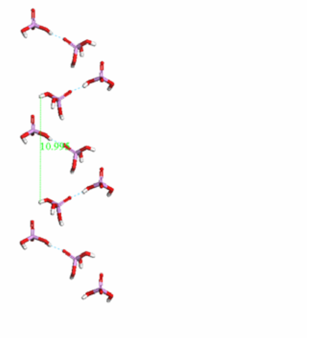


Figure S4. Helical nature of the hydrogen-bonded chain of phosphoric acid molecules. The pitch of the helix equals the length of the *b*-axis of 10.995Å.

4. Overlay of the calculated XRPD pattern based on single crystal structure of cocrystal and the capillary XRPD pattern of powder samples of cocrystal.

Powder samples of cocrystal was sealed in a 0.5mm quartz capillary tube, and powder X-ray diffraction data were collected on a Philips X-ray diffractometer equipped with a detector at 40 kV and 50 mA for Cu $K\alpha1$ (λ =1.5406Å) radiation monochromated by a 2-crystal Ge(220) 2-bounce monochromator.

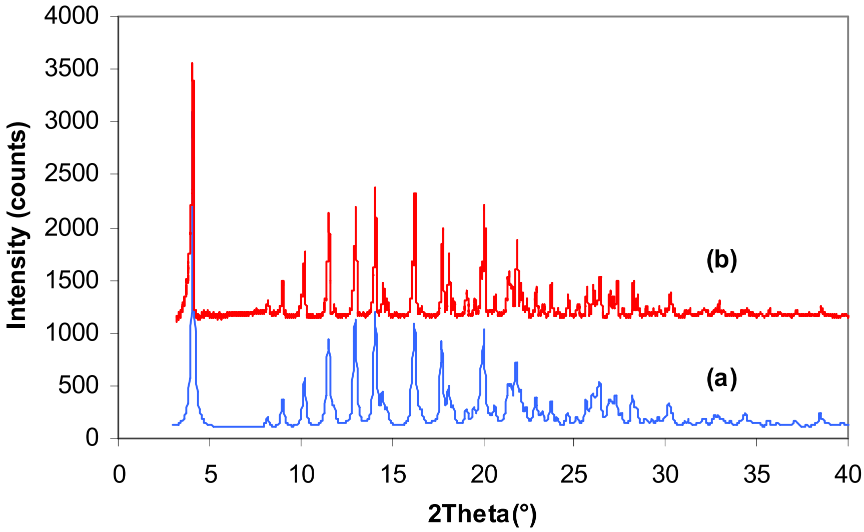


Figure S5. (a) Calculated XRPD pattern based on single crystal structure of cocrystal. (b) Capillary XRPD pattern of powder samples of cocrystal.

5. ^{15}N Liquid NMR data and experimental condition

^{15}N shifts (50.6 MHz) of Compound I·2H_3PO_4 were obtained from ^{1}H-^{15}N HMBC (long-range correlation) experiments using ca. 20mg/mL solutions in methanol-d_4 at -30°C and listed in Table S1. Attempts to obtain shift data for N-2 were unsuccessful (the piperazine ring protons were broad in a variety of solvents and temperatures). ^{15}N shifts are reported relative to external liquid NH_3 (δ_N=0ppm).

Table S1. ^{15}N Chemical shifts of Compound I·2H_3PO_4.

	δ_N(Compound I·2H_3PO_4) (ppm)
N-3	46(±0.5)
N-1	68
N-4	145