The Difluoromethylenephosphonate Moiety as a Phosphate Mimic: *X*-Ray Structure of 2-Amino-1,1-difluoroethylphosphonic Acid

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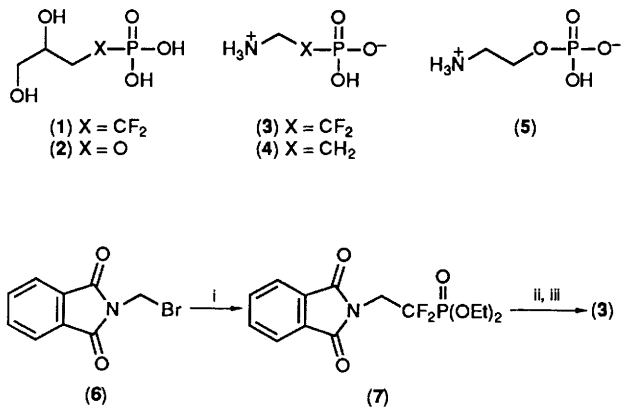
The synthesis and structure of 2-amino-1,1-difluorophosphonic acid (**3**) are described, providing the first *X*-ray crystal structure determination of a difluoromethylenephosphonate moiety; the structure allows an isosteric comparison to be drawn between the phosphate C–O–P bond angle and the phosphonate C–CF_2–P and C–CH_2–P bond angles with particular reference to the use of phosphonates as phosphate mimics in biological systems.

Several hydrolytically stable phosphonate analogues of phosphates have been shown to be substrates for appropriate enzymes.[1] The difluoromethylenephosphonate moiety has attracted attention recently as a potential streamlined isosteric and isoelectronic phosphate mimic.[2] It can be argued that introduction of two fluorine atoms onto the methylene carbon is more closely analogous to the bridging oxygen in C–O–P than the C–CH_2–P analogue. In earlier work from this laboratory we have shown that the difluoromethylenephosphonate analogue (**1**) of glycerol-3-phosphate (**2**) is a substrate for glycerol-3-phosphate dehydrogenase.[3] Other examples in the literature[2a,4] illustrate the success of difluoromethylenebisphosphonates as analogues of pyro- and tri-phosphates in enzymatic processes. Therefore to explore further the conformational and geometric comparison with the phosphate group it became appropriate to prepare a crystalline compound containing the difluoromethylenephosphonate moiety, for *X*-ray crystallography.

The target molecule 2-amino-1,1-difluorophosphonic acid (**3**) was chosen because its structure may be compared with the structures of 2-aminoethyl phosphate (**5**)[5] and 2-aminoethylphosphonic acid (**4**)[6] which have already been reported. Our synthetic route to (**3**) is illustrated in Scheme 1. The difluoromethylenephosphonate moiety was introduced by preparing an organozinc reagent as described by Burton and co-workers.[7] This reagent underwent a copper(I)-catalysed displacement of bromide when treated with *N*-bromomethylphthalimide (**6**) and the resulting product (**7**) was hydrolysed to give the free phosphonic acid, release of the phthalimido group from which using aqueous hydrazine gave



Scheme 1. *Reagents and conditions*: i, $BrCF_2PO(OEt)_2$, Zn powder, monoglyme, Cu^IBr, room temp., 10 h, 54%; ii, Me_3SiBr, 2 h then H_2O–ether (1:1), 75%; iii aq. NH_2NH_2, 60 h.

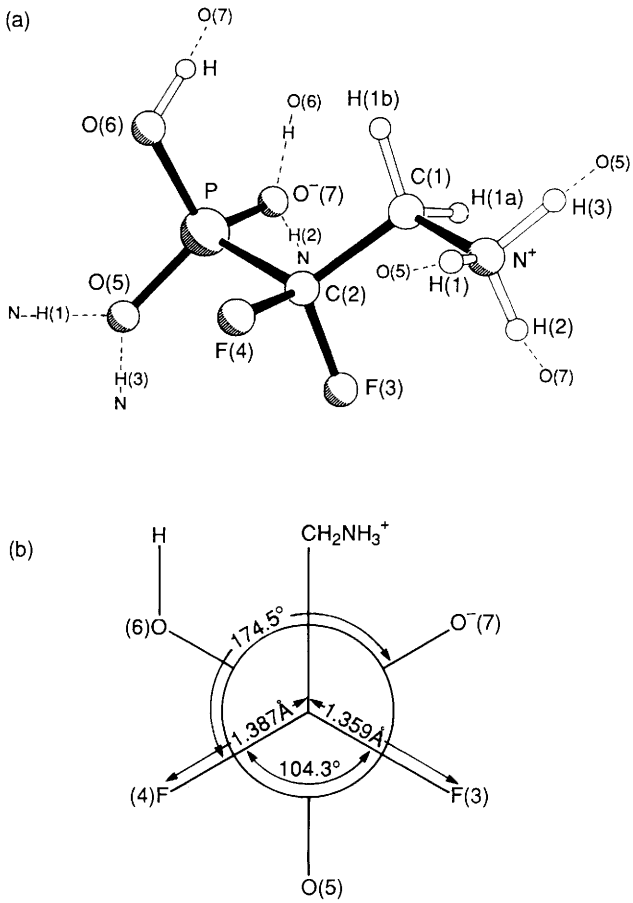


Figure 1. (a) Perspective view of the structure of (**3**). Intermolecular H bonds are indicated. Selected bond lengths (Å) and angles (°). P–O(6) 1.559(3); P–O(5) 1.484(2); C(2)–F(4) 1.387(4); C(1)–H(1b) 1.000(41); P–O(7) 1.498(3); P–C(2) 1.852(3); F(3)–C(2) 1.359(5); C(2)–C(1) 1.496(5); N–C(1) 1.483(4); C(1)–H(1a) 0.957(45); O(6)–P–O(7) 111.9(1); O(7)–P–O(5) 118.0(1); O(7)–P–C(2) 106.2(1); P–C(2)–F(4) 107.7(2); P–C(2)–C(1) 116.5(2); F(4)–C(2)–C(1) 108.3(3); H(1b)–C(1)–H(1a) 112.2(32); O(6)–P–O(5) 110.8(1); O(6)–P–C(2) 102.7(1); O(5)–P–C(2) 105.8(1); P–C(2)–F(3) 109.7(2); F(3)–C(2)–F(4) 104.0(3); F(3)–C(2)–C(1) 110.0(3); C(2)–C(1)–N 111.5(3). (b) Newman projection along C(2)–P.

(**3**), which was recrystallised from aqueous acetone to give colourless plates.†

† All intermediates gave satisfactory spectral data. Selected data for (**3**): ^1H NMR (D_2O) δ 3.59 (2H, td, $^3J_{HF}$ 17, $^3J_{HP}$ 1.4 Hz); ^{19}F NMR (D_2O) δ −119.95 ppm (dt, $^2J_{FP}$ 84.7, $^3J_{FH}$ 17.4 Hz); ^{31}P NMR (D_2O) δ 0.77 ppm (t, $^2J_{PF}$ 84.1 Hz); decomp. >304 °C.

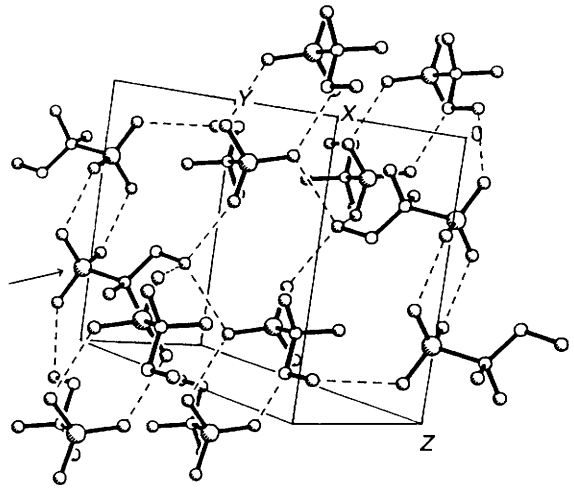


Figure 2. Stacking plot indicating the hydrogen bonding within the crystal lattice. Hydrogen atoms have been omitted for clarity.

The *X*-ray structure of the acid (**3**) is shown in Figure 1.‡ It is a zwitterion and assumes a *trans*-configuration around the C(1)–C(2) bond (∠PCCN 168.7°) similar to that of 2-aminoethylphosphonic acid (**4**) (∠PCCN 173.6°). Of significance is the C(1)–C(2)–P bond angle of 116.5° which is close to the phosphate C–O–P angle of 118.7° and can be compared with the C–CH_2–P angle in (**4**) of 112.1°. The widening of the C–CF_2–P angle and narrowing of the F–C–F angle (104.3°) is consistent with an increase in sp^2 character at C(2) in going from CH_2 to CF_2.[8] A Newman projection along the C(2)–P bond [Figure 1(b)] shows a staggered disposition of the fluorine atoms with respect to the phosphonate oxygen atoms.

‡ *Crystal data* for (**3**): $C_2H_6F_2NO_3P$, crystal (sealed in capillary) dimensions 0.6 × 0.3 × 0.05 mm, M = 161.04, monoclinic, space group $P2_1/n$, a = 5.425(1), b = 11.527(3), c = 9.226(2) Å, β = 91.95(2)°, Z = 4, D_c = 1.86 g cm^{-3}, $F(000)$ = 328, μ(Cu-K_α) = 4.30 mm^{-1}, R = 0.053, R_w = 0.059 for 725 reflections [$0 < 2\theta < 115°$, $I > 3.0\sigma(I)$, Nicolet R3m/V system, Cu-K_α *X*-radiation (graphite monochromator), λ = 1.54184 Å]. A weighting scheme of the form $w^{-1} = \sigma^2(F_o) + 0.001F_o^2$ gave a satisfactory analysis of variance. 780 unique data were used for the structure solution by direct methods (SHELXTL). Anisotropic vibrations were allowed for non-hydrogen atoms; all hydrogen atoms were located in successive difference maps but in the final refinement the hydrogens bonded to oxygen and nitrogen were included with constraints of O–H 0.85 and N–H 0.90 Å respectively. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

The C–F(4) bond (1.387 Å) is longer than the C–F(3) bond (1.359 Å) and is antiperiplanar to P–O(7) [F(4)–C(2)–P–O(7) 174.5°]. This increase in length may be attributed to a stereoelectronic n–σ* donation from O(7) to C(2). All the P–O bonds are shorter in (**3**) than those in their phosphonate (**4**) and phosphate (**5**) counterparts [*e.g.* P=O 1.484, 1.493, and 1.501 Å in (**3**), (**5**), and (**4**), respectively]. The bond length reductions in (**3**) are clearly due to the electronegative fluorine atoms. This pattern is consistent with the relative pK_a values for the second deprotonation of difluoromethylenephosphonates at 5.4—5.6,[9] phosphates at 6.2—6.25,[10] and phosphonates at 7.45.[10]

Perhaps surprisingly, the fluorine atoms are not involved in hydrogen bonding within the crystal lattice of (**3**) since the shortest intermolecular F–H bond is H(1b)–F(4), 2.649 Å. There is, however, extensive intermolecular hydrogen bonding between the amino and phosphonate groups. Each molecule has eight hydrogen bonds (Figure 1). Within the stacking plot in Figure 2 six of these can be seen clearly in the arrowed molecule.

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