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Unexpected formation of hydroxyborazaphosphonic acid in the reaction of (*N*-benzyl)benzylideneimine-2-boronic acid with diethyl phosphite

Agata Rydzewska [a], Katarzyna Ślepokura [b], Tadeusz Lis [b], Paweł Kafarski [a], Piotr Młynarz [a,*]

[a] Department of Bioorganic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland
[b] Faculty of Chemistry, University of Wrocław, 14 F. Joliot-Curie St., 50-383 Wrocław, Poland

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ABSTRACT

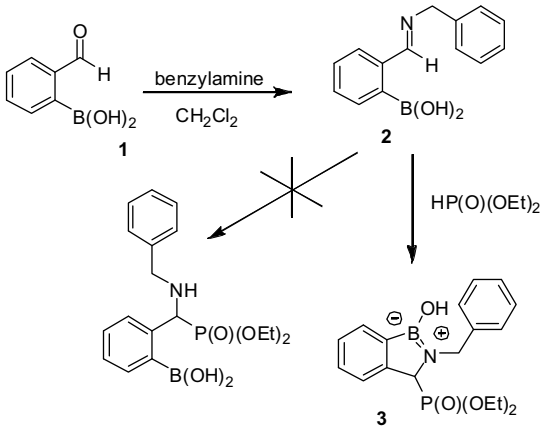
During the synthesis of an aminobenzylphosphonic acid bearing a boronic acid group at the ortho position, surprisingly, formation of hydroxyborazaphosphonic acid occurred. This compound appeared to be unstable in protic solvents.

Boronic acids have found important applications in organic chemistry. They are useful reagents, catalysts and intermediates in organic synthesis.[1–7] Also, they are interesting building blocks used in supramolecular and analytical chemistry due to their ability to complex carbohydrates, catechols, amino acids and metal ions.[8–11] They also serve as analogues of transition states of proteolytic enzymes, which permit their application in medicine as exemplified by the useful anticancer agent, Bortezomib, acting as a proteasome inhibitor.[12,13] In addition, they find application in crystal engineering, which is due to the electron deficient character of the boronic group.[14]

During our efforts to obtain aminobenzylphosphonic acids functionalized with a boronic moiety at position 2 of the aromatic ring, the formation of a non-trivial hydroxyl-boraza-aromatic fragment was unexpectedly obtained. This structure is rare in organic chemistry, with examples being hydroxyborazaphenanthrene derivatives.[15–17]

Thus, 2-formylphenylboronic acid (**1**) was converted into the corresponding Schiff base by refluxing with benzylamine in methylene chloride for 7 h. After removal of the volatile components, the resulting crude (*N*-benzyl)benzylideneimine-2-boronic acid (**2**) was reacted with diethyl phosphite in toluene. Removal of toluene and slow crystallization from ethyl acetate resulted in a crystalline product **3**, which was obtained in 46% yield.[18]

The structure of compound **3** was identified by X-ray analysis.[19–22] Although this compound is chiral, it crystallizes in a centrosymmetric space group, which means that both enantiomers are



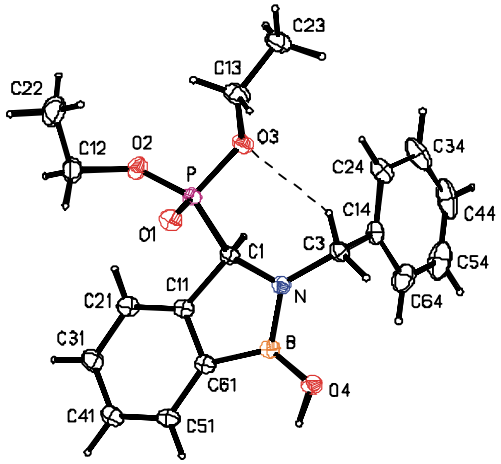


Figure 1. The X-ray crystal structure and the atom numbering scheme for one of the enantiomers present in the crystal **3**. Displacement ellipsoids are shown at the 40% probability level. The intramolecular C–H···O contact is shown with a dashed line.

* Corresponding author. Tel./fax: +48 71 3204597.
E-mail address: piotr.mlynarz@pwr.wroc.pl (P. Młynarz).

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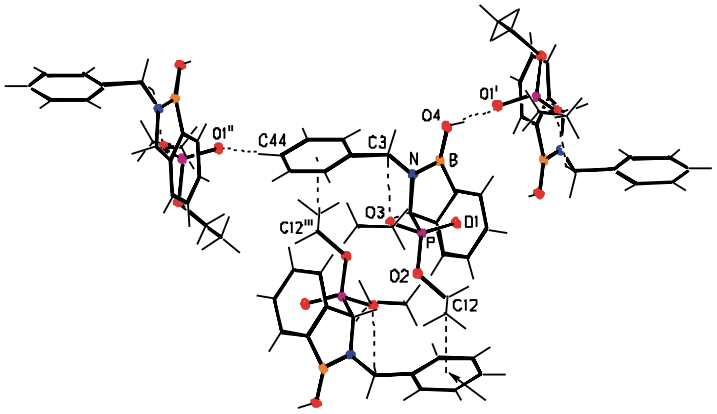


Figure 2. The arrangement of the molecules in the crystal of compound **3**. Dashed lines show intra- and intermolecular C–H···O close contacts and intermolecular O–H···O and C–H···π interactions. The geometry: H4···O1^{i} 1.80(2) Å, O4···O1^{i} 2.688(2) Å, O4–H4···O1^{i} angle 175(2)°; H44···O1^{ii} 2.54 Å, C44···O1^{ii} 3.359(2) Å, C44–H44···O1^{ii} angle 144°; H12B···π^{iii} 2.57 Å, C12···π^{iii} 3.545(3) Å, C12–H12B···π[*Cg*(Ph)]^{iii} angle 167°. *Cg*(Ph) is the centroid of the phenyl ring. Symmetry codes: (i) $-x+3/2$, $y-1/2$, $-z+3/2$; (ii) x, $-y+1$, $z-1/2$; (iii) $-x+1$, $-y+1$, $-z+1$.

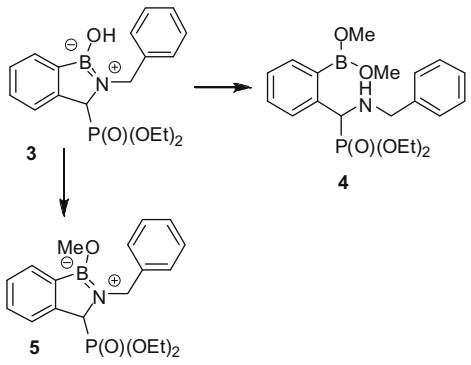
present in the crystal. One of them is shown in Figure 1. Both the N and B atoms are in planar, trigonal environments, which makes the whole heterocyclic moiety planar, with the root mean square deviation of the fitted atoms equal to 0.021 Å. The B–N, B–O4, B–C61, N–C1 and N–C3 bond distances are 1.427(2), 1.359(2), 1.563(2), 1.468(2) and 1.460(2) Å, respectively, and are typical for such atoms in these environments.[19,20] This is consistent with Bsp^2–Nsp^{2}p(π)–p(π) interactions with formal negative and positive charges on B and N, respectively.

Due to the high annular tension in the five-membered ring, some of the bond angles deviate significantly from 120°, with the highest deviations observed for C51–C61–B [134.5(2)°], C11–C61–B [106.6(2)°], O4–B–C61 [132.6(2)°] and N–B–C61 [106.0(2)°]. Both the hydroxyl O4–H4 and methylene C3 atoms lie in the plane of the heterocyclic system, which is twisted at 83.6(1)° relative to the C14–C64 phenyl ring. The geometry at the phosphonate P atom [P–O1 1.474(2), P–O2 1.574(2), P–O3 1.574(1), P–C1 1.820(2) Å, O1–P–O2 113.60(7)°, O1–P–O3 115.16(6)°, O2–P–O3 104.40(6)°, O1–P–C1 114.02(5)°, O2–P–C1 105.95(5)°, O3–P–C1 102.53(6)°] is deformed from the ideal tetrahedral shape, which is a common feature of the phosphonate groups.[21] The molecular structure of the compound is stabilized by an intramolecular hydrogen bond between C3–H3B···O3 (Fig. 1): the H3B···O3 and C3···O3 distances are 2.41 and 3.099(2) Å, and the C3–H3B···O3 angle is 126°. Adjacent molecules are joined to each other by intermolecular O4–H4···O1^{i} and C44–H44···O1^{ii} contacts, in which the phosphonate O1 atom acts as a bifurcated acceptor. The crystal structure is additionally stabilized by intermolecular centrosymmetric C12–H12B···π[*Cg*(Ph)]^{iii} interactions, giving rise to a three-dimensional network. The packing mode and the arrangement of the molecules within the crystal lattice, along with the geometrical details and the symmetry codes of the intermolecular interactions, are shown in Figure 2.

NMR studies in DMSO confirm the structure determined by crystallography. However, in spectra recorded in $CDCl_3$, three phosphorus signals were observed. This might be a result of dimerization due to dehydratation or hydrogen bonds formation.

The lack of a dimeric structure in the ESI-MS spectrum in acetonitrile seemed to exclude these possibilities. However, an adduct of compound **3** with one molecule of acetonitrile was clearly seen when using both positive and negative ionization modes. When ESI-MS was performed in a 1:1 mixture of DMSO and methanol, a molecular ion peak for compound **3** was observed at *m/z* 358(−) accompanied by peaks at *m/z* 428(+) suggesting formation of compound **4** (sodium salt) and at *m/z* 396(+), which most likely derives from the formation of the sodium salt of compound **5**. When studies were performed in pure methanol, similar results were obtained.

In conclusion, this observation confirms the fact that compound **3** readily reacts with methanol reflecting equilibria between compounds **3**, **4** and **5**. In water, decomposition of compound **3** was observed by ESI-MS.



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18. Compound **3**: ^{1}H NMR (DMSO [d_6], 600 MHz, δ (ppm)): 1.08 and 1.15 (t, J = 7.1 Hz, 3H each), 3.78–3.98 (m, 4H), 4.22 (d, J_{H-P} = 11.7 Hz, 1H), 4.51 and 4.76 (d, J = 15.2 Hz, 1H each), 7.15–7.23 (m, 3H), 7.29–7.37 (m, 4H), 7.47 (d, J = 7.1, 1H), 7.75 (d, J = 7.1, 1H), 8.66 (s, 1H). ^{13}C NMR (DMSO [d_6], 151 MHz, δ (ppm)): 17.06 (d, J_{H-P} = 5.33 Hz), 17.21 (d, J_{H-P} = 5.33 Hz), 46.98, 59.16 (d, J_{H-P} = 150.47 Hz), 62.81 (d, J_{H-P} = 7.2 Hz), 62.11 (d, J_{H-P} = 7.3 Hz), 124 (d, J_{H-P} = 2.0 Hz), 127.71 broad signal, 127.36, 128.28, 128.47 (d, J_{H-P} = 1.1 Hz), 129.36, 139.76, 147.34 (d, J = 4.6 Hz). ^{13}P NMR (DMSO [d_6], 243 MHz, δ (ppm)): 22.89. ^{11}B NMR (DMSO [d_6], 193 MHz, δ (ppm)): 28.50.
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21. Colourless crystals; mp 149–151 °C; the crystallographic measurement was performed on a *Kuma KM4CCD* automated four-circle diffractometer with graphite-monochromatized MoK_α radiation. Data for the crystal were collected at 140(2) K using an *Oxford Cryosystems* cooler and corrected for Lorentz and polarization effects. Data collection, cell refinement data reduction and analysis were carried out with KM4CCD software (Oxford Diffraction Poland): CRYSALIS CCD and CRYSALIS RED, respectively, [KM4CCD software: CRYSALIS CCD and CRYSALIS RED, Oxford Diffraction Poland, 1995–2003]. No analytical absorption correction was applied. The structure was solved by direct methods using the SHELXS-97 program and refined by a full-matrix least-squares technique using SHELXL-97 [Sheldrick, G. M. *Acta Crystallogr.*, **2008**, *A64*, 112] with anisotropic thermal parameters for all non-H atoms. All H atoms were found in difference Fourier maps. In the final refinement cycles, the C-bonded H atoms were treated as riding atoms, with C–H distances of 0.95–1.00 Å, and with U_{iso} values of 1.2U_{eq} (CH, CH_2) or 1.5U_{eq} (CH_3). The hydroxyl H atom was refined with U_{iso} = 1.5U_{eq}(O). The figures were generated using the XP program [XP—Interactive molecular graphics—ver. 5. 1—Bruker Analytical X-ray Systems, 1998**]**.
22. Compound **3**: $C_{18}H_{23}BNO_4P$, M = 359.15, colourless block, crystal dimensions: 0.55 × 0.50 × 0.50 mm^3; monoclinic, space group $C2/c$; a = 20.788(9), b = 10.097(5), c = 20.355(9) Å, β = 118.88(5)°; V = 3741(3) Å^3; T = 140(2) K; Z = 8; ρ_{calc} = 1.275 g cm^{-3}; μ = 0.168 mm^{-1} (for Mo Kα, λ = 0.71073 Å); F(000) = 1520; reflections collected = 18,935; reflections independent = 6970 [R_{int} = 0.0284]; reflections observed = 4604 [$I > 2\sigma(I)$]; θ range 3.60–36.65°; h, k, l range: $-27 \leqslant h \leqslant 31$, $-16 \leqslant k \leqslant 13$, $-33 \leqslant l \leqslant 27$; full-matrix least-squares on F^2; parameters = 229; restraints = 0; R_1 = 0.0458; wR_2 = 0.1149 [$F_o^2 > 2\sigma(F_o^2)$]; GooF = S = 1.012; largest difference in peak and hole, $\Delta\rho_{max}$ and $\Delta\rho_{min}$ = 0.52 and −0.25 e Å^{-3}. CCDC 700809 contains supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or by e-mailing deposit@ccdc.cam.ac.uk.