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Evidence for strong heterodimeric interactions of phenylboronic acids with amino acids

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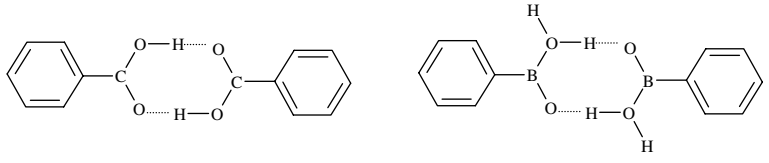
This letter is dedicated to Professor Roland Boese (University of Duisburg-Essen) on the occasion of his 60th birthday

Abstract—Strong heterodimeric interactions of phenylboronic acids with L-proline or betaine are evident in the solid state. The interaction energy is over 23 kcal/mol (at MP2/6-31+G*).

Apart from new perspectives in organic chemistry, for example, in Suzuki coupling reactions,[1] boronic acids have recently gained wide applications in the fields of biochemistry and medicinal chemistry.[2] There is strong interest in the synthesis of new derivatives since they are used as boron neutron capture therapy (BNCT) agents,[3] as antibiotics,[4] enzyme inhibitors,[5] for treatment of tumors[3,6] and as saccharide sensors.[7] These applications stimulate continuing investigations on their physicochemical properties, especially to understand better the mechanism of molecular interactions with biologically active systems.[8] Following work on molecular recognition, phenyl boronic acids have recently been employed as promising building blocks in crystal engineering[9,10] and various types of novel supramolecular assemblies have been generated.[9a,11]

Boronic acids possess a $-B(OH)_2$ functional group. Analogous to carboxylic acids, they are capable of forming dimeric units. In fact, this is the most basic and frequent structural motif found in the solid state.[12] The energies of the carboxylic and boronic acid dimers are comparable (−19.3 kcal/mol and −12.9 kcal/mol for dimers A and B, respectively, see Scheme 1).[10] Due to the close similarity between the $-B(OH)_2$ and –COOH groups, efforts have been made to synthesize the heterodimeric hydrogen-bonded motifs.[10,13–15] The energy of a mixed dimer is somewhat in between the value for carboxylic and boronic acid dimers (−15.4 kcal/mol), but the charged system Ph-$B(OH)_2\cdots^{-}$OOC-Ph was predicted to be very stable (−42.8 kcal/mol).[10] This kind of structure has been recently obtained by Höpfl and co-workers[10] in complexes of phenylboronic acids with



A B

Scheme 1.

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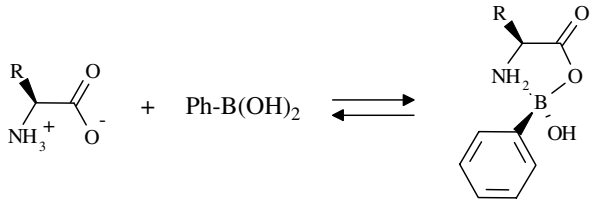
tetrabutylammonium benzoate. The tetrabutylammonium cation is a bulky species, which helps in efficient charge separation. As a consequence, a charge-assisted boronic acid–carboxylate interaction is formed, which displays high geometric complementarity. The supramolecular assemblies of 4-carboxyphenylboronic acids with 4-dimethylaminopyridine, 4-acetylpyridine oxime, and 2-methyl imidazole provide further evidence that the carboxylate–boronic acid synthon is capable of competing successfully in a range of well-known interactions.[15]

Amino acids are probably the most important building blocks in nature. They occur in different states of protonation, depending on the pH and the local environment. Mohler and Czarnik[16] postulated that, as with carbohydrates,[17] they form a chelate structure with a boronic acid, where boron is tetracoordinated, as shown in Scheme 2. Another possible structure can be formed when proton transfer occurs. In the zwitterionic form, the carboxylate group is negatively charged, which facilitates heterodimeric interactions. This motif has been found in betaine boronate[14] and phenylalanine 3,5-bis(trifluoromethyl)phenylboronic acid 18-crown-6, a three component supramolecule.[13] The purpose of this communication is to show that, (i) phenylboronic acids form heterodimeric complexes with amino acids, which exist without synergistic action of any other species, and (ii) that the interactions in the complexes are strong.

Two complexes with L-proline or betaine, that have the expected molecular architecture were prepared. L-Proline is a natural amino acid, where the side chain is covalently bonded to the amino group, which in consequence significantly affects the structure of a peptide (or a protein). This hydrophobic fragment is often found in the position where a protein collapses. Betaine, in turn, is a model for the simplest amino acid (glycine) but with a fully induced zwitterionic form. This reference compound was used to analyze the efficiency of interactions in the dimeric complex. Among many available phenylboronic acids the expected assemblies were formed by the *p*-ethoxy derivative. The complex structures were obtained by co-crystallization of 1:1 molar ratios of *p*-ethoxyphenylboronic acid with L-proline or betaine, from ethanol.



Scheme 2.

The asymmetric part of the triclinic crystal lattice of the complex of L-proline with *p*-ethoxyphenylboronic acid (L-PEBA) consists of two units of the complex. The molecules are oriented to form asymmetric heterodimers, as shown in Figure 1. The O···O distances are quite short (2.664, 2.706 and 2.701, 2.718 Å, for the two complexes, respectively), which suggests that the interactions between the acids in the dimer are strong. A closer inspection reveals that the dominant dimeric motif is immersed in a rich network of weaker hydrogen bonds, that form infinite chains: each amino site of L-proline interacts with one (or two) carboxylate groups of neighboring L-prolines, and with one hydroxy group of the boronic acid (with N···O distances in the range 2.855–2.975 Å). Due to the close proximity of the two heterodimeric units, the $-B(OH)_2$ groups are twisted away from the phenyl plane (by 8.7–15.0°) while the carboxylate groups are twisted with respect to the boronic fragments by 17.3° and 27.5°. In consequence, the dimers are non-planar, and this weakens the dimer.

The hydrogen bond network stabilizes the crystal structure of L-PEBA, however, the most interesting heterodimeric motif is obscured. This is not the case with the molecular complex of *p*-ethoxyphenylboronic acid with betaine (BEBA). Despite the different crystallographic system (a monoclinic unit cell), this complex also con-

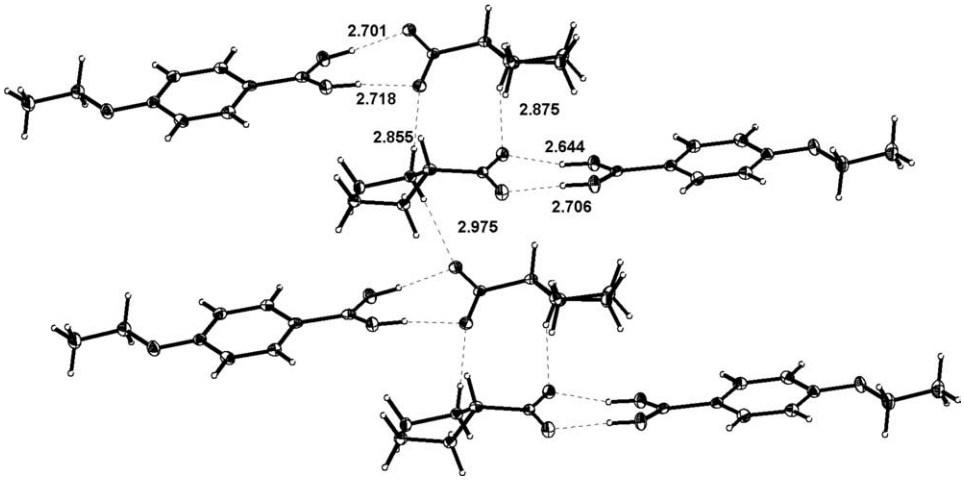


Figure 1. The intermolecular interactions in the crystal lattice of L-PEBA. The numbers denote O···O distances. The displacement ellipsoids are drawn at the 50% probability level.

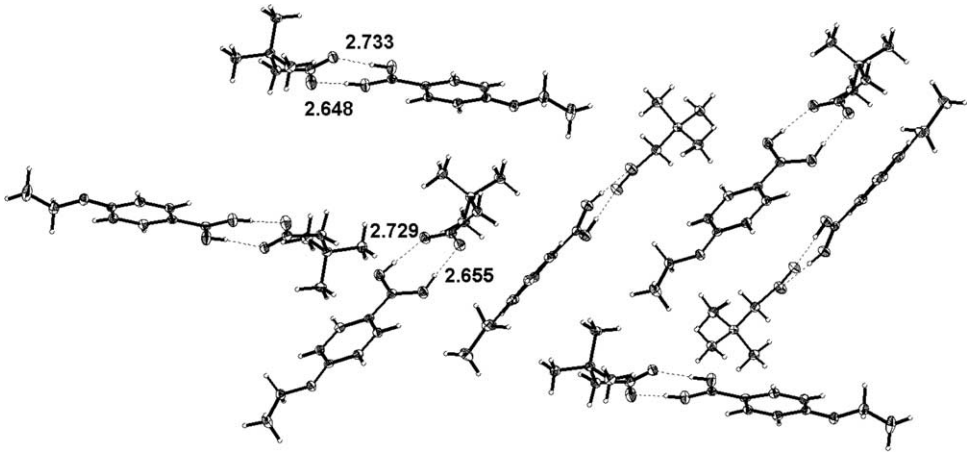


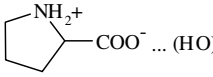
Figure 2. The intermolecular interactions in the crystal lattice of BEBA. The numbers denote O···O distances. The displacement ellipsoids are drawn at the 50% probability level.

sists of two independent units in an asymmetric part (see Fig. 2). As might be expected, the molecules form heterodimers of very similar geometry and they are not perturbed by additional hydrogen bonds in the crystal lattice. These dimers are much more asymmetric compared with L-PEBA (with O···O distances of 2.648, 2.733 and 2.655, 2.729 Å for the two complexes, respectively, see Fig. 2), which can be implied by the close proximity of oppositely charged centers in the betaine fragment. The carboxylate and boronic fragments are twisted to a smaller extent as compared with the relevant species of L-PEBA (by 12.7° and 15.2°). Also, the $-B(OH)_2$ groups are twisted from the phenyl plane to a much smaller degree (by 1.5° and 16.7°) as compared with L-PEBA.

Starting from the experimental geometries, we have optimized the molecular complex of L-proline with phenylboronic acid, and the complexes of betaine with phenylboronic acid and its *p*-ethoxy and *p*-nitro derivatives at the MP2/6-31+G* level of theory.[18] In the ab initio optimized structure of the proline complex, the amino acid fragment is additionally stabilized by an intramolecular interaction between the carboxylate group and the amino site (see the supplementary information), which in turn underestimates the strength of the heterodimeric interaction. On the other hand, all the betaine complexes became planarized during the optimization process approaching C_s symmetry and the interaction energies were estimated for the planar arrangement. By substituting the methyl groups by hydrogen atoms it was also possible to estimate the energies of the respective glycine complexes having the same symmetry (C_s). These complexes were also optimized at the MP2/6-31+G* level. The basis-set superposition error (BSSE) corrected interaction energies, calculated via the supermolecular approach,[19] for the dimers are given in Table 1.

Even though these values are estimates of the interaction energies in the condensed phase, the energies in the range of 23–28 kcal/mol suggest strong heterodimeric interactions between the phenylboronic acids and amino

Table 1. The BSSE corrected interaction energies for the proline complex and for the betaine complexes with boronic acids

Dimeric system	E_{int} (kcal/mol)
	−23.1
$(CH_3)_3N^+CH_2COO^-\cdots(HO)_2BPh$	−25.5 (−23.4)
$(CH_3)_3N^+CH_2COO^-\cdots(HO)_2BC_6H_4OC_2H_5$	−24.9 (−22.9)
$(CH_3)_3N^+CH_2COO^-\cdots(HO)_2BC_6H_4NO_2$	−28.6 (−26.3)

The values in brackets are given for respective glycine complexes.

acids. As expected, the electronic nature of the substituent in the phenyl fragment plays an important role in the stability of the complex, with electron-accepting substituents (the nitro group) favoring stronger interactions (by ca. 3 kcal/mol) than electron donors (the ethoxy group).

We consider that these structures of the complexes are of fundamental value in understanding the role of phenylboronic acids in studies of molecular recognition of biologically active systems. The interaction energies indicate that the formation of heterodimers with amino acids should be an efficient process, which is controlled (at least to some extent) by the nature of the substituent and the conformation of the phenyl fragment. The latter can easily accommodate the steric requirements of a protein active site.

We are aware that this is not the only motif that can be realized and that a synergistic action of other species may provide an even more complicated picture. The structure of a typical protein (or peptide) is dominated by complex systems of hydrogen bonds, many of which have partially ionic character. This environment is extremely favorable for strong heterodimeric interactions.

Crystal data: data collection, cell refinement and data reduction were carried out with the Kuma Diffraction programs: CrysAlis CCD and CrysAlis RED.[20] The data were corrected for Lorentz and polarization

effects, but no absorption correction was applied. The structures were solved by direct methods[21] and refined by using SHELXL.[22] **L-PEBA**: $C_{13}H_{20}BNO_5$, $M = 281.11$, triclinic $P1$, $a = 7.376(1)$ Å, $b = 7.830(1)$ Å, $c = 12.959(1)$ Å, $\alpha = 84.11(1)$, $\beta = 78.72(1)$, $\gamma = 73.91(1)$, $V = 704.3(1)$ Å^3, $T = 100(2)$ K, $Z = 2$, $D_x = 1.326$ mg/m^3, $F(000) = 300$, absorption coefficient μ(Mo-Kα) = 0.1 mm^{-1}, the collected data range was $3.21 < \Theta < 24.99$ deg. ($-8 \leqslant h \leqslant 8$, $-9 \leqslant k \leqslant 9$, $-15 \leqslant l \leqslant 15$), 9931 reflections measured, 4709 unique ($R_{int} = 0.0619$), which were used in all calculations. The final R and $wR(F_2)$ were, respectively, 0.0528 and 0.1430 (all data), 0.0525 and 0.1423 (for 4665 $I > 2\sigma(I)$), maximum and minimum difference electron densities were 0.303 and -0.376 eÅ^{-3}. **BEBA**: $C_{13}H_{22}BNO_5$, $M = 283.13$, monoclinic $P2_1/n$, $a = 19.222(2)$, $b = 9.179(1)$, $c = 19.337(2)$, $\beta = 118.76(1)$, $V = 2991.1(6)$, $T = 100(2)$ K, $Z = 8$, $D_x = 1.257$ mg/m^3, $F(000) = 1216$, absorption coefficient μ(Mo-Kα) = 0.094 mm^{-1}, the collected data range was $2.54 < \Theta < 25.00$ deg. ($-22 \leqslant h \leqslant 21$, $-10 \leqslant k \leqslant 10$, $-22 \leqslant l \leqslant 22$), 20617 reflections measured, 5219 unique ($R_{int} = 0.0302$), which were used in all calculations. The final R and $wR(F_2)$ were, respectively, 0.0522 and 0.1107 (all data), 0.0386 and 0.1007 (for 4005 $I > 2\sigma(I)$), maximum and minimum difference electron densities were 0.200 and -0.205 eÅ^{-3}. Crystallographic data (excluding structure factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 277519 and CCDC 277520. These data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

Supplementary data associated with this article (containing the optimized geometries of the dimers studied) can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.105.

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