

Solubility of phenylboronic compounds in water

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Abstract: Solubility of six phenylboronic compounds in water was investigated using different methods. The results are consistent with each other, although for particular compounds selected methods should be preferred. The solubility of the investigated compounds is low, with the value of ca. 2 g/100 cm³ H₂O at 20°C for unsubstituted phenylboronic acid. The unsubstituted benzoxaborole is less soluble than phenylboronic acid. Introduction of OiBu, COOH and CF₃ groups into the phenyl ring decreases solubility in comparison with unsubstituted phenylboronic acid, especially for the alkoxy substituent.

Keywords: Solubility, solid-liquid equilibrium, boronic, phenylboronic acid, benzoxaborole.

Introduction

Boronic acids are the compounds of growing interest not only for Suzuki coupling reaction ¹, but also due to their wide applications in catalysis, medicine and biology ². A great interest has been also paid to the supramolecular systems formed by these compounds in which two hydroxyl groups can be involved in various homomeric and heteromeric hydrogen-bonded assemblies, leading to the important compounds applied in materials' chemistry ³. Recently, rising research activity was directed to benzoxaboroles, internal hemiesters of phenylboronic acids, due to their exceptional properties leading to new applications in biology, medicine and materials' chemistry ⁴.

The solubility data are crucial for purification and formulation of new biologically active compounds. Many important reactions require the choice of the right solvent and reaction conditions, especially temperature. Suzuki–Miyaura cross-coupling is the most widely used protocol for the formation of the carbon-carbon bond and has become significant method in the synthesis of biaryl compounds, resulting in a wide range of pharmaceuticals. Among the various sustainable media, water is an attractive solvent for this reaction due to its low cost, non-flammability, non-toxicity, and environment friendliness ⁵.

Taking into account the above-mentioned numerous applications of boronic compounds, there are surprisingly few results of their solubility in water and organic solvents. Even for the known for about 150 years phenylboronic acid, only 2 values of its solubility in water at 0°C and 25°C have been published so far ⁶. One can also find some

generalized and misleading statements in the literature such as “boronic acids are water soluble” ⁵ or “since the reactants are insoluble in water” ⁷. For benzoxaboroles there are even less information: only general statement like “[benzoxaboroles] show a better solubility profile “without any data given” ⁸.

The aim of the present work is to investigate the solubility of boronic acids and benzoxaboroles in water. Since our earlier research on the solubility of organoboron compounds in organic solvents ⁹ were focused on different systems, it was necessary to find an appropriate method to determine solubility of these classes of compounds in water. The oldest and frequently used dynamic (synthetic) method with the visual detection of crystals' disappearance ^{9a} failed for the investigated systems. Several methods (A - C) have been selected and obtained results compared in terms of consistency of obtained data. Advantages and disadvantages of application of the methods in this particular system have been discussed, taking into account possible sources of measurement errors.

Experimental Section

Materials

Phenylboronic acid (**1**) was obtained from Alfa Aesar and was recrystallized from water before use. The following compounds have been synthesized by the procedures described elsewhere: **2** ¹⁰, **4** ¹¹. Compounds **3**, **5** and **6** have been synthesized from the corresponding aryl bromides according to the typical procedure described in ¹².

Methods of solubility determination

Method A. Dynamic method with the use of luminance probe ¹³

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Mixture of solute and solvent, prepared by weighing pure components, were heated to dissolve the solid. The measurements were conducted using the apparatus described by Hofman et al.¹³, in which LED was the source of light and luminance was measured using the LP 471 LUM 2 probe (Photo-

Radiometer HD2102.1). Measured temperatures and light intensities were acquired independently and transformed into the light intensity versus temperature dependence. A typical observed dependence noted for the phenylboronic acid + water system is shown in Figure 1.

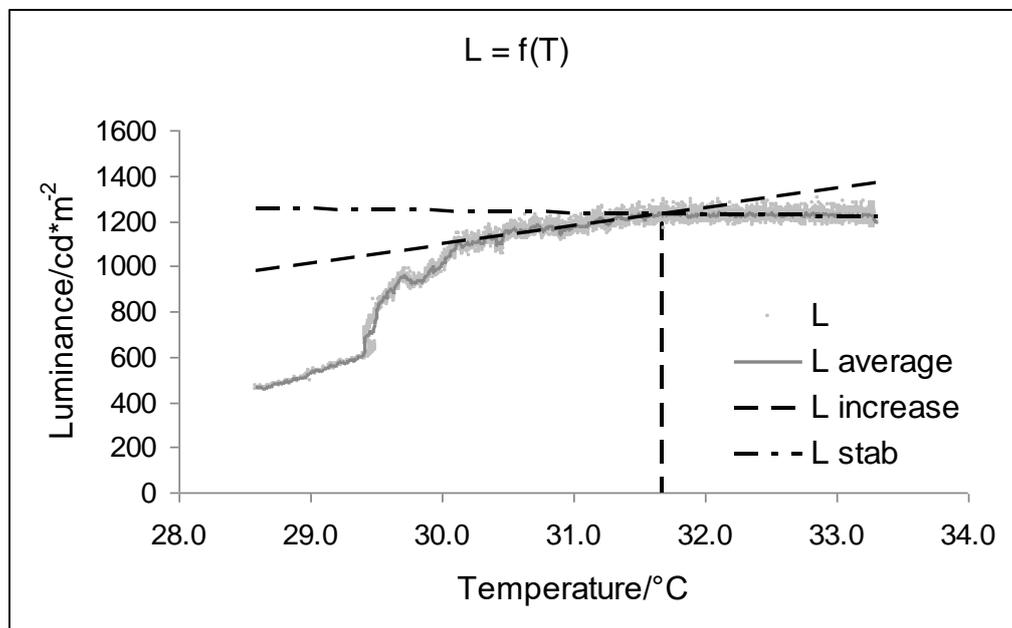


Figure 1. Luminance vs. temperature plot for phenylboronic acid **1** in water.

Method B. Conductometric method¹⁴

The measurements were conducted by the method originally described by Rogalski et al. for determination of solubility of phenols in water¹⁴. Weighted amounts of the boronic compound and water were placed in the conductivity sample cell. The cell was designed to minimize vapor volume to avoid the partial vaporization at elevated

temperatures. The amount of solute was in excess with respect to saturation. The solution was stirred for 2 h at a temperature sufficiently high to solubilize all of the solute and cooled to precipitate the solute. The mixture was stirred for 2 h at the measurement temperature before starting conductivity measurements.

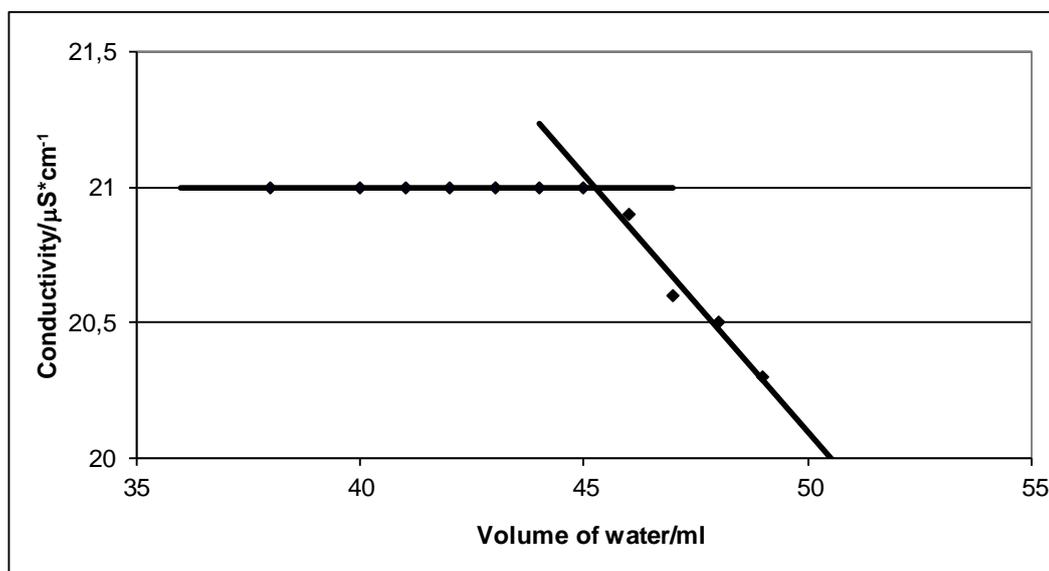


Figure 2. Conductance vs. volume of water plot for the compound **3** at 40°C.

The excess solute was dissolved by injecting known volumes of water (from 0.5 to 2.5 cm³). After each injection, the solution was vigorously stirred for about 20 min to ensure thermal and chemical equilibrium. The stirring was stopped before every measurement. Repeated measurements for each added volume allow to check if the equilibrium was reached (the same conductance values for two measurements). Typical plot of conductance vs. volume of the solvent for a constant temperature is shown in Figure 2.

Method C. Isothermal (static) method

The suspension of solute in water was stirred at constant temperature for about 4 h to reach equilibrium. After sedimentation of the solid a saturated solution was sampled, weighed and evaporated at 90°C to reach a constant mass of the solid. For a given temperature, each determination was repeated to obtain similar results. The presented data are the mean values for each temperature.

Results and Discussion

Solubility of the boronic compounds in water was investigated for the compounds shown in Chart 1.

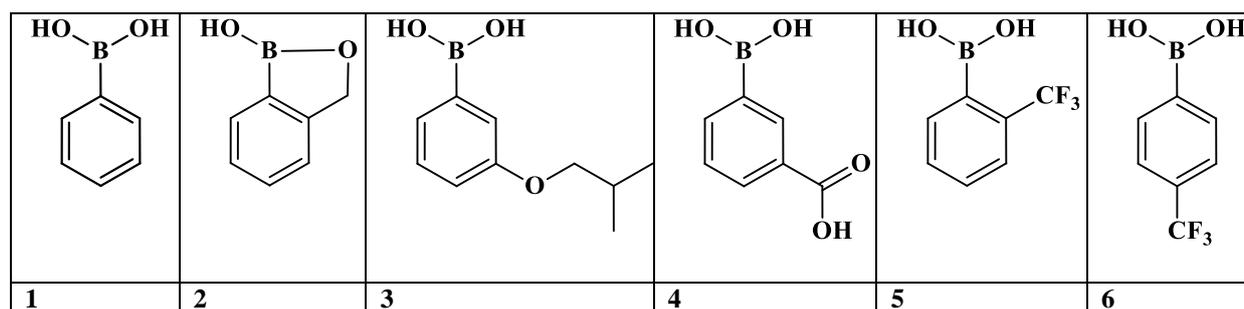


Chart 1. Boronic compounds investigated in the present paper.

Solubility of phenylboronic acid (1) determined by methods A - C is shown in Figure 3.

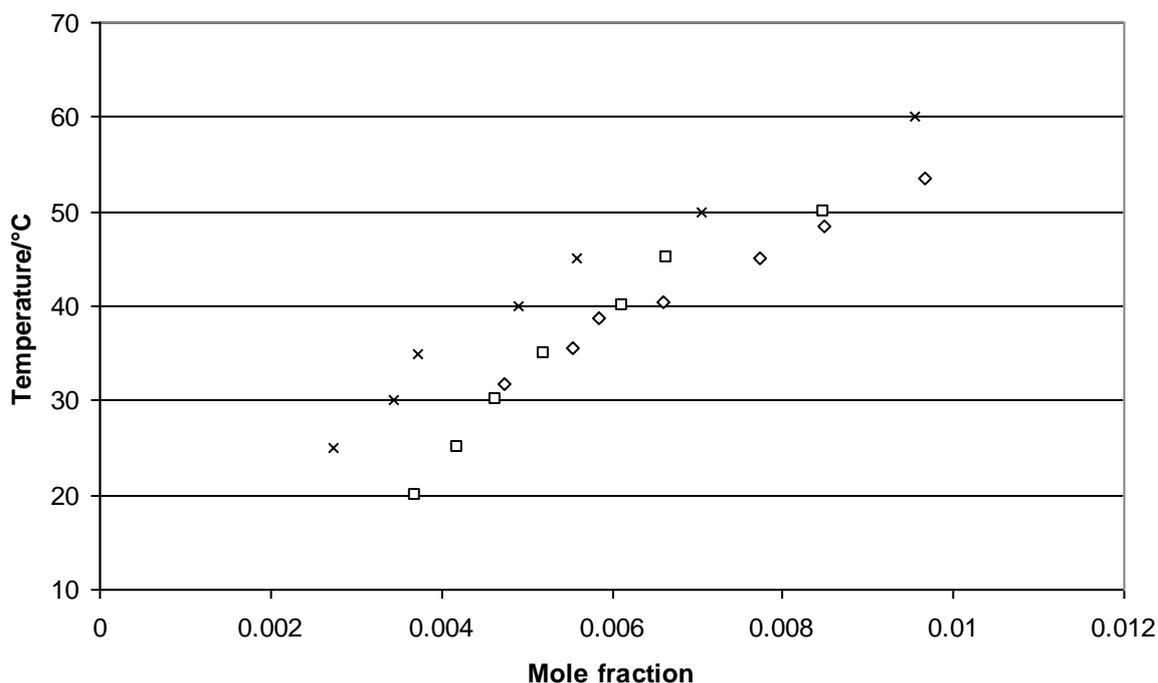
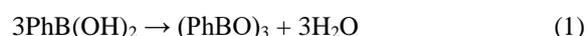


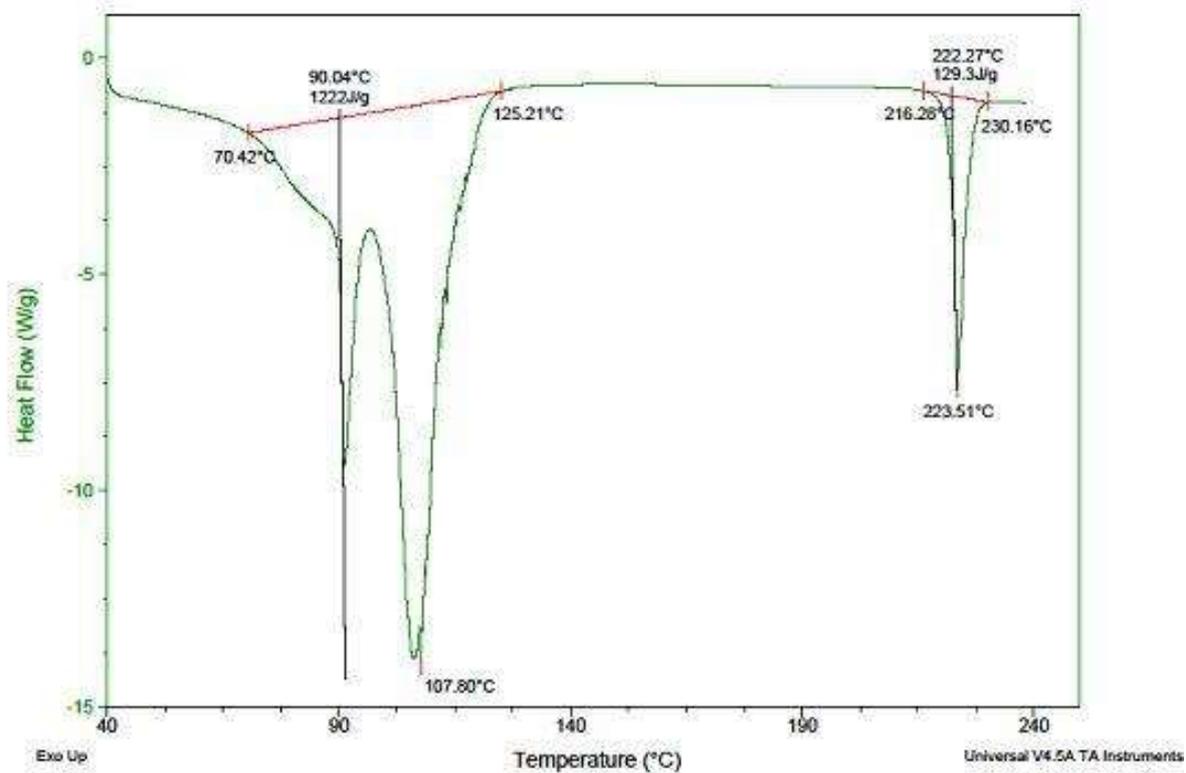
Figure 3. Solubility of phenylboronic acids (1) in water. ◇ Method A, □ method B, x method C.

Lower values obtained by method C can be caused by the formation of boroxine during evaporation of the solvent at 90°C according to Eq. 1:

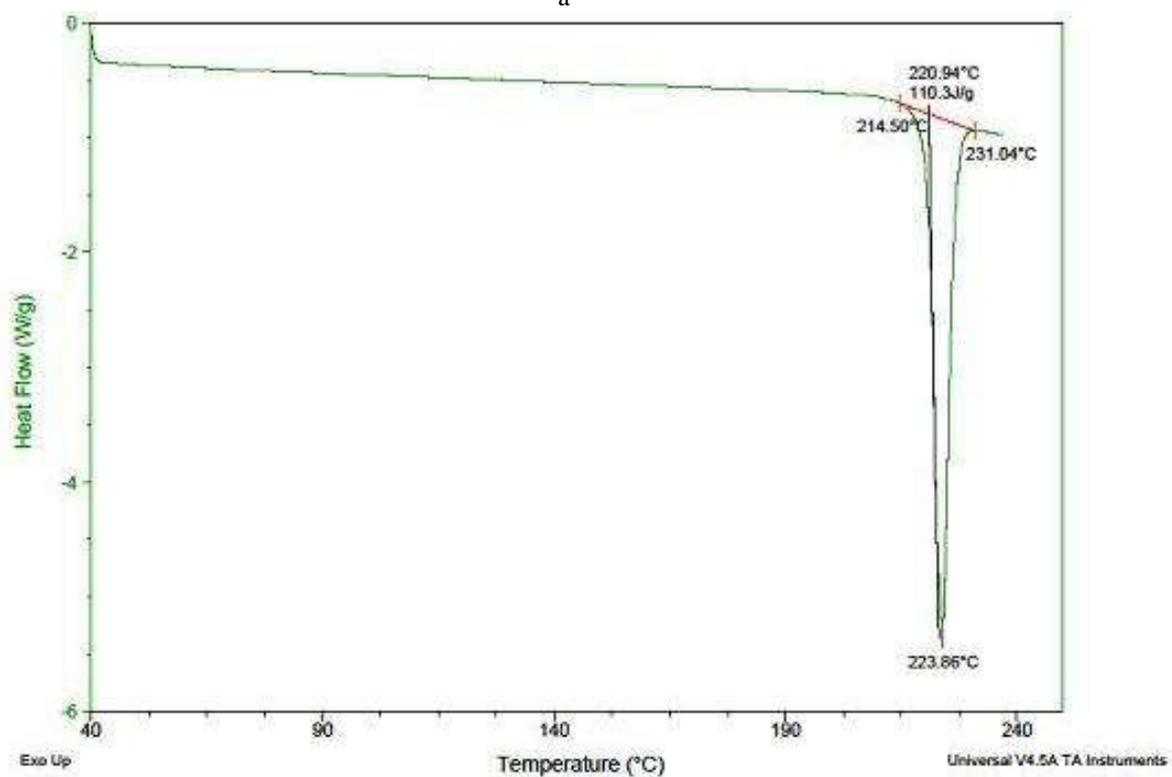


The formation of cyclic anhydrides (boroxines) by boronic acids is a well-known feature of these

compounds. The acid/boroxine equilibrium depends on the substituents in the aryl group. DSC measurements of the p-methoxyphenylboronic acid confirm that the fast dehydration starts at about 90°C¹⁵. However, some compounds dehydrate easily during standing on air at room temperature. DSC curve for unsubstituted phenylboronic acid (1) and for the corresponding boroxine is shown in Figure 4.



a



b

Figure 4. DSC plot for phenylboronic acid (1) (a) and triphenylboroxine (b).

Solubility of benzoxaborole (2) is shown in Figure 5.

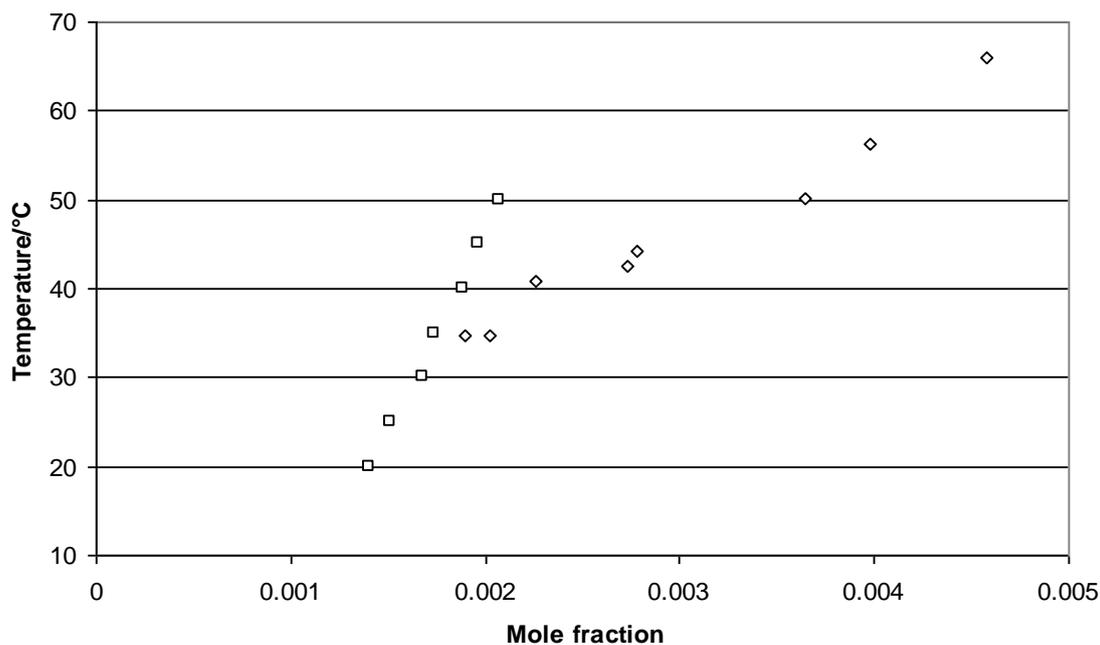


Figure 5. Solubility of benzoxaborole (2) in water. ◇ Method A, □ method B.

In order to investigate the influence of substituents on the solubility of boronic acids in water we

investigated compounds 3 - 6. The results are shown in Figures. 6 - 9.

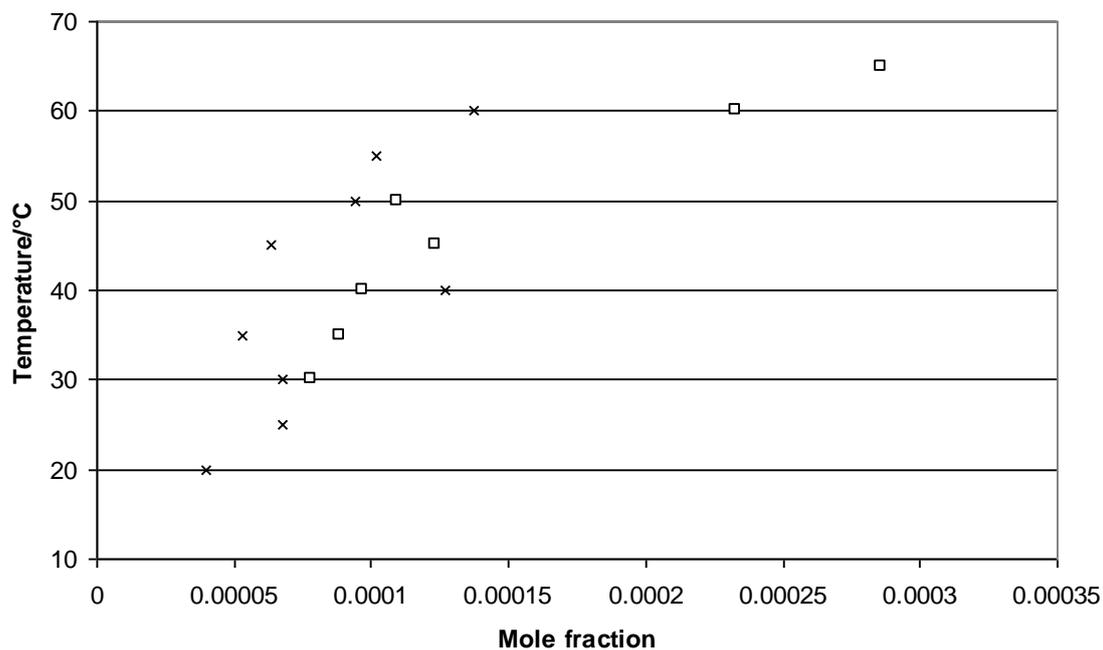


Figure 6. Solubility of 3-isobutoxyphenylboronic acid (3) in water. □ Method B, x method C.

Introduction of alkoxy substituent in compound 3 decreases solubility in water. Moreover, a much larger spread of results is visible for this compound, especially applying the method C. The difficulties of solubility determination for this type of compound can be also caused by the possibility of aggregation

in aqueous solution into variety of structures like micelles, vesicles, and more complex ones¹⁶.

Solubility of other compounds (4 - 6) in water was determined by the method C. The results are shown in Figures 7 - 9.

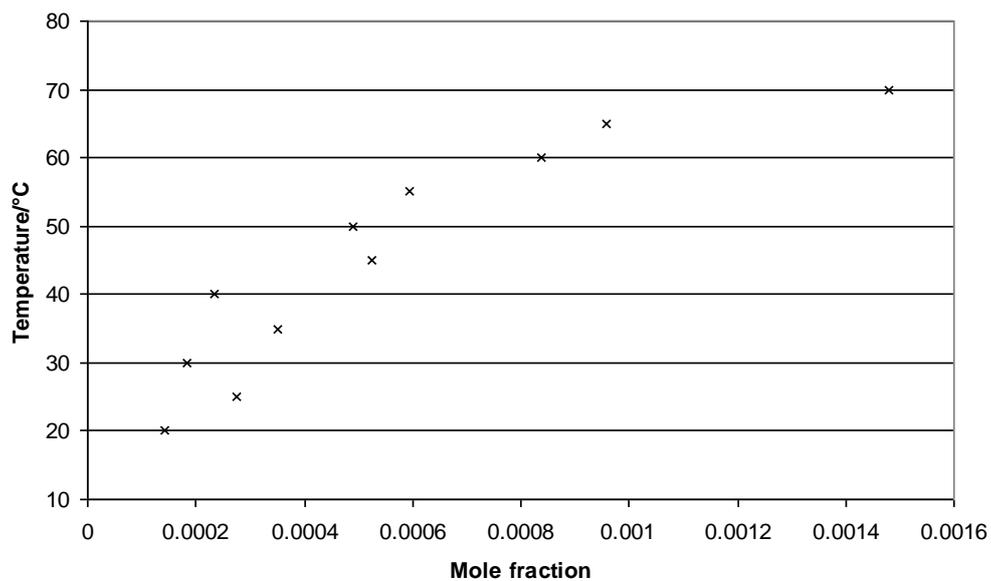


Figure 7. Solubility of 3-carboxyphenylboronic acid (4) in water.

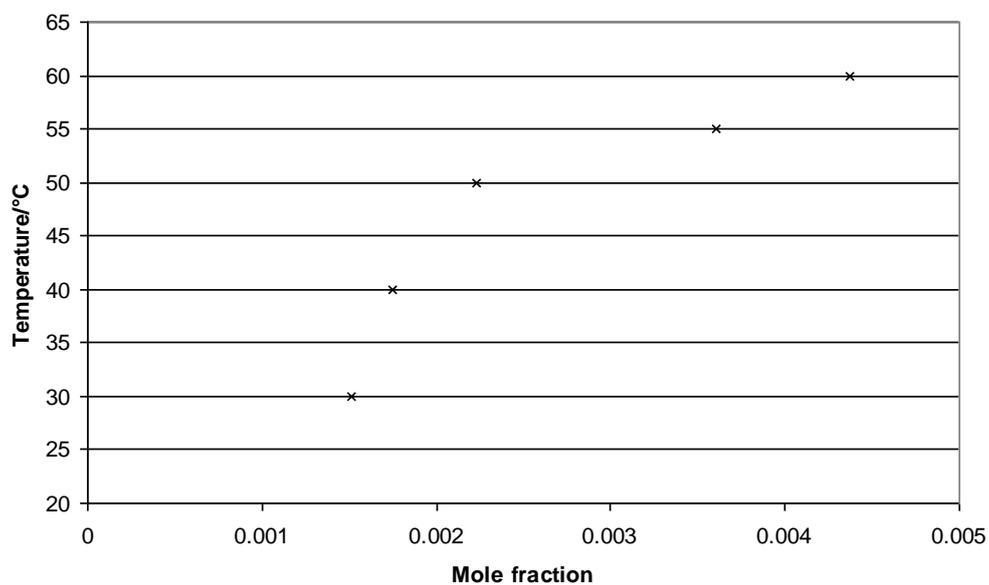


Figure 8. Solubility of 2-(trifluoromethyl)phenylboronic acid (5) in water.

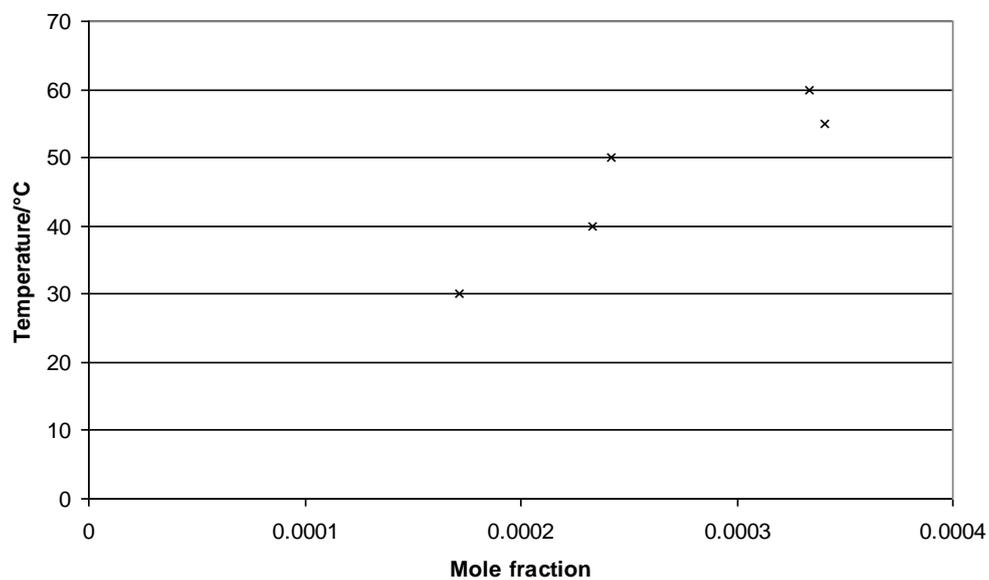


Figure 9. Solubility of 4-(trifluoromethyl)phenylboronic acid (6) in water.

Comparison of solubility of investigated compounds is shown in Figure 10.

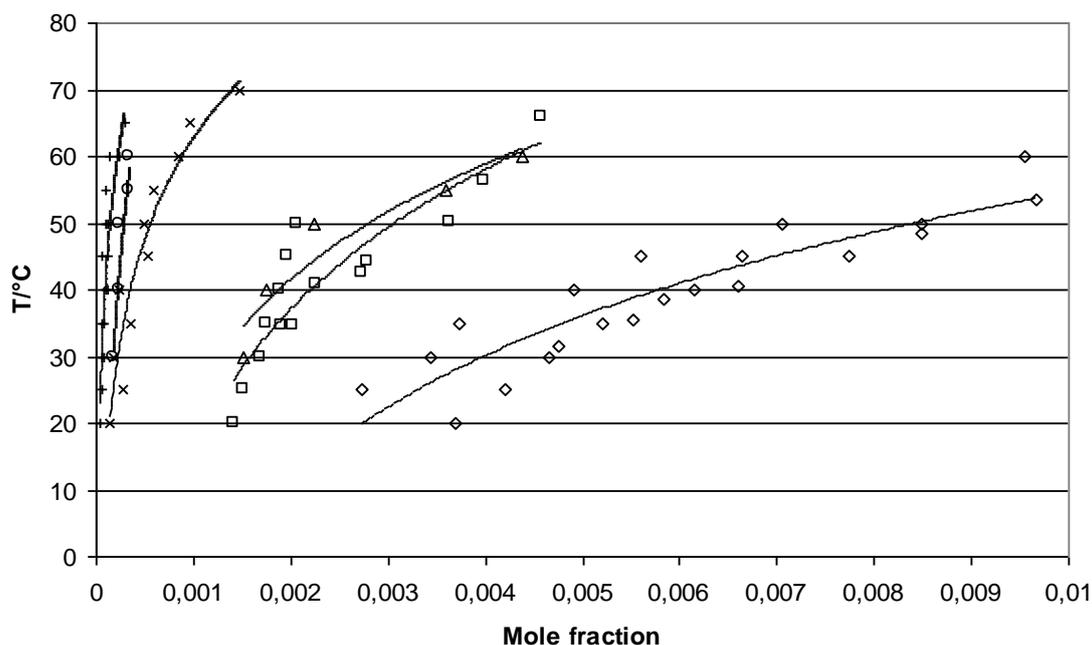


Figure 10. Solubility of investigated compounds in water. \diamond Phenylboronic acid (1), \square benzoxaborole (2), + 3-isobutoxyphenylboronic acid (3), \times 3-carboxyphenylboronic acid (4), Δ 2-(trifluoromethyl)phenylboronic acid (5), \circ 4-(trifluoromethyl)phenylboronic acid (6). Solid lines represent logarithmic trend lines.

The solubility of investigated compounds in g/100 g H₂O at 20.0°C and 50.0°C is collected in Table 1.

Table 1. Solubility in water in g/100 g H₂O for selected temperatures, calculated from the curves in Figure 10.

Compound	Temperature/°C		Standard deviation
	20.0	50.0	
1	1.86	5.75	0.025
2	0.84	2.27	0.021
3	0.04	0.15	0.0017
4	0.13	0.51	0.0043
5	0.80	2.67	0.0236
6	0.12	0.26	0.0018

All the primary experimental data are collected in Supplementary Data.

Conclusions

1. All the applied methods of solubility investigations give comparable results. However, the selection of the appropriate method depends on particular compound.
2. Phenylboronic acid (1) shows the best solubility in water. Benzoxaborole (2) is less soluble than 1.
3. Introduction of OiBu, COOH and CF₃ groups causes decrease of solubility in comparison with 1.
4. *ortho*-Isomer of (trifluoromethyl)phenylboronic acid (5) is less soluble than *para*-isomer 6.
5. Significant change of solubility with temperature allows to use water as crystallization solvent.

Acknowledgement

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