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SOLVENT EXTRACTION OF CATECHOLS WITH BORON-CONTAINING REAGENTS

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Three types of boron-containing solvent extraction reagents, 4-(di-2-ethylhexylamido) phenylboronic acid, 4-(di-2-ethylhexylamino-methyl)phenylboronic acid, and 1-tetradecylboronic acid, were synthesized and tested for the solvent extraction of catechol, resorcinol and hydroquinone. All of these reagents extracted catechol highly selectively over other catechols, resorcinol and hydroquinone.

1. Introduction

In recent years, much attention has been focused on brain science, particularly with regard to information communication via neural systems which has been of much interest. In such system, neurotransmitters like catecholamines, acetylcholine, serotonin and so on

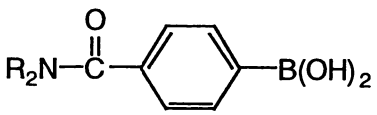
play important roles and information communication is based on complex molecular recognition of neural system receptors for these neurotransmitters. Consequently, the recognition of catechol moieties is very important from the point view of neuro science. In addition, much attention has been paid also to the various types of polyphenol compounds such as catechin, flavones contained in natural materials like green tea, various herbs, red wine, maidenhair tree leaves, and so on from the point of view of human health. Since the majority of these natural polyphenol compounds consist of catechol moieties, recognition of catechol is important in relation not only to the molecular recognition of these polyphenol compounds but also to the recovery and concentration of these compounds from natural materials.

It is well known that boronic acid has a high recognition ability for two hydroxyl groups existing at the α-position. For the purpose of separation and purification of sugar proteins, various types of adsorbents containing the functional groups of boronic acid with high affinity or high recognition ability for hydroxyl groups at the α-position have been developed recently. These adsorbents are considered to be have a high affinity not only for sugars but also for catechol compounds. Therefore, we prepared 3 types of boron-containing solvent extraction reagents as shown in Fig. 1 and qualitatively tested the extraction behavior for 3 types of catechols: catechol, resorcinol, and hydroquinone in the present work.

2. Experimental

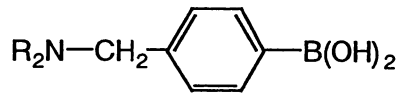
2.1 Synthesis of the reagents

Two of the reagents employed in the present work, 4-(di-2-ethylhexylamido)-phenylboronic acid and 4-(di-2-ethylhexylaminomethyl)phenylboronic acid, abbreviated as



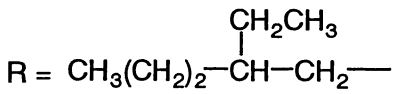
4-(Di-2-ethylhexylamido)
phenylboronic acid

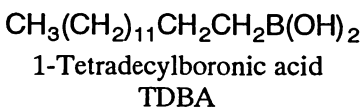
DEHAmidoPBA



4-(Di-2-ethylhexylaminomethyl)
phenylboronic acid

DEHAminoPBA





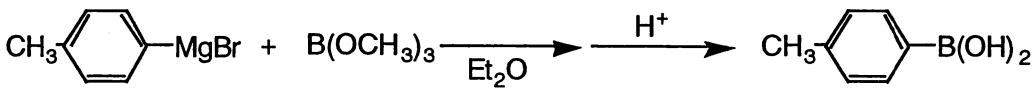
1-Tetradecylboronic acid
TDBA

Fig.1 Chemical structures of the solvent extraction reagents developed in the present work.

DEHAmidoPBA and DEHAminoPBA, respectively, hereafter, were synthesized from 4-methylphenylboronic acid.

2.1.1 Synthesis of 4-methylphenylboronic acid[1-3)]

4-Methylphenylboronic acid was synthesized according to the following reaction.

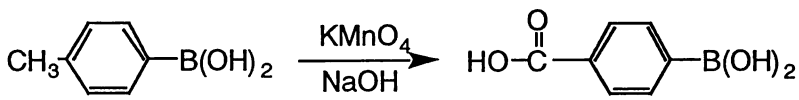


Twelve g (0.49 mol) of magnesium and 100 cm^3 of dry ether together with a small amount of iodine were taken and refluxed together. During the reflux, 68.6 g (0.40 mol) *p*-bromotoluene dissolved in 180 cm^3 dry ether and, subsequently, 370 cm^3 dry ether were added dropwise to prepare bromo-*p*-tolylmagnesium. After cooling below –60 ℃, 37.4 g (0.44 mol) trimethylborate dissolved in 90 cm^3 dry ether was added dropwise vigorously

stirring for 1 h. After further stirring for 1 h, the temperature was slowly raised to room temperature and the reaction was continued for a further 4 h. Then, the trimethylborate product was hydrolyzed at 0 ℃ to 4-methylphenylboronic acid by adding dilute sulfuric acid. Then, desired compound was extracted with ether. The extract was washed with a saturated brine solution and dried over anhydrous magnesium sulfate. After filtration and evaporation, the residue was dissolved in water by heating to remove yellow impurities. The filtrate was cooled to obtain white needle crystals; 28.4 g (52.3%); $\nu_{O\text{-}H}$ 3200-3400 cm^{-1} (br), $\nu_{B\text{-}O}$ 1366 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$, TMS, 20°C) δ 2.4 (3H, s, CH_3), 7.3 (2H, d, ArH-C), 8.1 (2H, d, ArH-B).

2.1.2 Synthesis of 4-carboxyphenylboronic acid[3,4)]

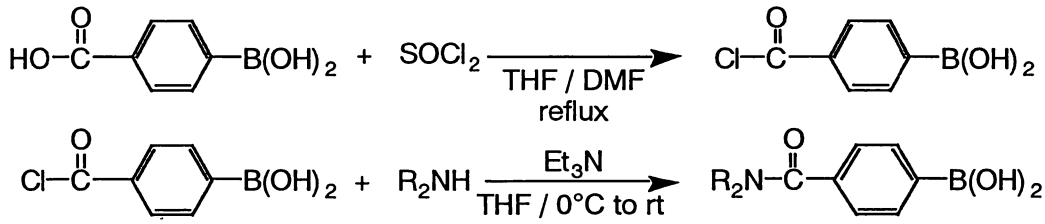
4-Carboxyphenylboronic acid was synthesized according to the following reaction from 4-methylphenylboronic acid.



Ten g (73 mmol) of 4-methylphenylboronic acid and 6.0 g of sodium hydroxide dissolved in 400 cm^3 water were vigorously stirred. Potassium permanganate, 24.4 g (154 mmol), dissolved in 300 cm^3 water was added dropwise to this mixture at 40 ℃ at a rate such that the color of the added potassium permanganate was immediately reduced. At the later stage of the addition, the temperature of the reaction mixture was gradually raised and, after addition was complete, the mixture was stirred at 50-60 ℃ for 1 h. After decomposing the unreacted potassium permanganate by adding 5 cm^3 of ethanol, the MnO_2 precipitate was removed by filtration. The volume of the filtrate was then reduced. Subsequently, 20 cm^3 of concentrated hydrochloric acid was slowly added at room

temperature to obtain the crystalline 4-carboxyphenylboronic acid. Crude crystal was further purified by recrystallization from water to obtain white needle crystals; 6.1 g (50.4%); ν_{O-H} 2700-3500 cm^{-1} (br), $\nu_{C=O}$ 1700 cm^{-1}, ν_{B-O} 1358 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$, TMS, 20°C) δ 7.95 (4H, s, ArH), 12.6-13.0 (1H, s(br), COOH).

2.1.3 Synthesis of DEHAmidoPBA[4)]



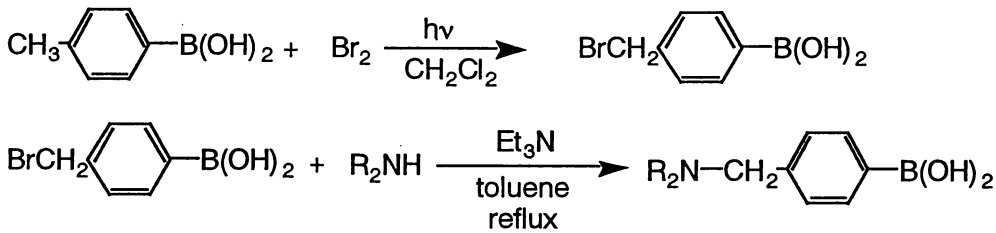
DEHAmidoPBA was synthesized from 4-carboxyphenylboronic acid according to the reaction shown above.

To three hundred cm^3 of anhydrous tetrahydrofuran containing 10.0 g (60 mmol) of 4-carboxyphenylboronic acid was added several drops of dimethylformamide. After rapidly adding 25 cm^3 (345 mmol) of thionylchloride at room temperature, the mixture was refluxed for 90 min, then excess thionylchloride and the solvent were removed by evaporation. The precipitate was dissolved again in dry tetrahydrofuran and 30.4 g (30 mmol) of triethylamine were slowly added dropwise and, subsequently, 11.6 g (48 mmol) of di-2-ethylhexylamine was also added at 0 ℃. After the dropwise addition, the mixture was stirred for 4 h in an ice bath and, subsequently, at room temperature for 5 h. From the mixture, an insoluble solid was separated by filtration and the solvent was removed by evaporation to obtain a brown viscous liquid, which was dissolved in ethyl acetate and washed sequentially with dilute hydrochloric acid, saturated brine solution, dilute sodium bicarbonate solution and finally with saturated brine solution again. The organic layer was

dried over anhydrous magnesium sulfate and evaporated. Although it was confirmed by thin layer chromatography that some impurities were contained in the crude product, it was used in the solvent extraction test work without further purification; $\nu_{O\text{-}H}$ 3200-3500 cm^{-1} (br), $\nu_{C\text{-}H}$ 2930 cm^{-1}, $\nu_{C=O}$ 1600 cm^{-1}, $\nu_{B=O}$ 1250-1380 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$, TMS, 20°C) δ 0.64 (6H, t, 2 x $\underline{CH_3}(CH_2)_3$), 0.86 (6H, t, 2 x $\underline{CH_3}CH_2$), 1.40 (18H, m, 2 x $\underline{CH(CH_2)_3}$+$CH_3\underline{CH_2}$), 3.18 (4H, d, 2 x NCH_2), 7.44 (2H, d, ArH-C), 8.32 (2H, d, ArH-B).

2.1.4 Synthesis of DEHAminoPBA[5)]

DEHAminoPBA was synthesized also from 4-methylphenylboronic acid via 4-bromomethylphenylboronic acid according to the following reaction.



4-Methylphenylboronic acid (10.16 g, 74.8 mmol) was dissolved in 450 cm^3 of dry dichloromethane. To the mixture, 7.6 g (95 mmol) of bromine dissolved in 50 cm^3 dry dichloromethane was added dropwise while being irradiated by 300 W incandescent light. The mixture was stirred for 3 h and the solvent was removed by evaporation. The residue was washed with hexane and filtered to obtain a pale yellow precipitate, which was dissolved in chloroform for recrystallization to obtain a pale yellow powder. Although the product contained a small amount of the feed material, this product was used in the next step.

4-bromomethylphenylboronic acid (3.5 g, 16.3 mmol) was dissolved in 150 cm^3 of

toluene and 1.7 g (48.9 mmol) triethylamine and 3.94 g (16.3 mmol) of di-2-ethylhexylamine dissolved in 40 cm^3 of toluene was slowly added dropwise at 60 ℃. After the dropwise addition, the mixture was refluxed for 48 h. After the reaction, it was cooled to room temperature and insoluble solid particles were removed by filtration. To the filtrate, ethyl acetate was added and the mixture washed with dilute hydrochloric acid 4 times, with distilled water twice, and finally with saturated brine solution. Solvent was removed by evaporation to obtain a brown viscous liquid; ν_{O-H} 3200-3500 cm^{-1} (br), ν_{C-H} 2930 cm^{-1}, $\nu_{B=O}$ 1378 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$, TMS, 20°C) δ 0.78 (6H, t, 2 x $\underline{CH_3}(CH_2)_3$), 0.87 (6H, t, 2 x $\underline{CH_3}CH_2$), 1.20 (16H, m, 2 x CH_2-N), 1.20 (2H, m, 2 x $\underline{CH}(CH_2)_3$), 2.13 (4H, d, 2 x N-CH_2), 3.43 (2H, s, 2 x N-CH_2-Ar), 7.26 (4H, d, ArH-C +ArH-B).

2.1.5 Synthesis of 1-tetradecaneboronic acid[1-3)]

1-Tetradecaneboronic acid, abbreviated as TDBA hereafter, was synthesized according to the following reaction.

$$RMgBr + B(OC_4H_9)_3 \xrightarrow[THF]{} \xrightarrow{H^+} R-B(OH)_2$$

Magnesium (2.8 g, 111 mmol) , 200 cm^3 of dry tetrahydrofuran and a small amount of iodine were mixed and refluxed. During the reflux, 25 g (90 mmol) of 1-bromotetradecane dissolved in 75 cm^3 of dry tetrahydrofuran were added dropwise and, subsequently, 350 cm^3 of dry tetrahydrofuran to prepare bromotetradecylmagnesium. The mixture was cooled to –60 ℃ to precipitate Grignard reagent and 18.9 g (82 mmol) of tributylborate dissolved in 50 cm^3 dry tetrahydrofuran was added dropwise for 1 h with vigorous stirring. Then, the temperature was increased to room temperature and the

mixture was further stirred for 4 h to complete the reaction. Dilute sulfuric acid was added at 0 ℃ for hydrolysis. After the residue was dissolved in ether, the mixture was washed with saturated brine solution and dried over anhydrous magnesium sulfate. From the mixture, solvent was removed by evaporation and a pale yellow liquid was obtained. It was added to 95 % ethanol, which was stirred at room temperature and kept in a freezer at –30 ℃ for 1 day. The white precipitate was removed by filtration and the filtrate was evaporated. To the residue, was added petroleum ether and this was kept in a refrigerator for 1 day to obtain a white powder; 7.51 g (34.5%); ^{1}H-NMR (270 MHz, $CDCl_3$, TMS, 20°C) δ 0.87 (3H, t, 2 x $\underline{CH_3}CH_2$), 1.28 (22H, m, $CH_3(\underline{CH_2})_{11}$), 1.56 (2H, m, $\underline{CH_2}CH_2B$), 3.74 (2H, s(br), $CH_2\underline{CH_2}B$).

2.2 Solvent extraction tests

Solvent extraction tests were carried out batchwise at 30 ℃ for 3 types of catechols, i.e. catechol, resorcinol and hydroquinone, using the 3 types of the above-mentioned reagents and di-2-ethylhexylamine, abbreviated as DEA hereafter, for comparison. Organic phases were prepared by diluting these reagents in analytical grade diluent to the required concentration, where chloroform was used as the diluent for DEHAmidoPBA and TDBA while hexane was used for DEHAminoPBA.

Aqueous solutions of these catechols were prepared by dissolving reagent grade catechol, resorcinol or hydroquinone individually deionised water to the required concentration. In the test to examine the effect of pH, the pH value was adjusted by adding a small amount of 1 mol dm^{-3} hydrochloric acid or sodium hydroxide solution. The concentration of these catechols was measured by means of spectrochemical analysis using a Shimadzu type UV-160 UV-visible spectrophotometer at the wave length of 275, 276

and 288 nm for catechol, resorcinol or hydroquinone, respectively, at pH = 5.5.

Ten ml of the organic and aqueous phases were placed in a 50 cm^3 stoppered flask and shaken in a water bath incubator maintained at 30 ℃ for 2 h to attain equilibrium. The concentrations of catechols in the aqueous phase before and after the equilibrium were measured as described earlier.

3. Results and Discussion

Figure 2 shows the relationship between the concentrations of 3 kinds of catechols in organic and aqueous phases after the extraction with only chloroform containing no reagent. Although the extraction of resorcinol and hydroquinone can be neglected, small amount of catechol is extracted with chloroform alone. On the other hand, it was found that not only resorcinol and hydroquinone but also catechol are not appreciably extracted in hexane.

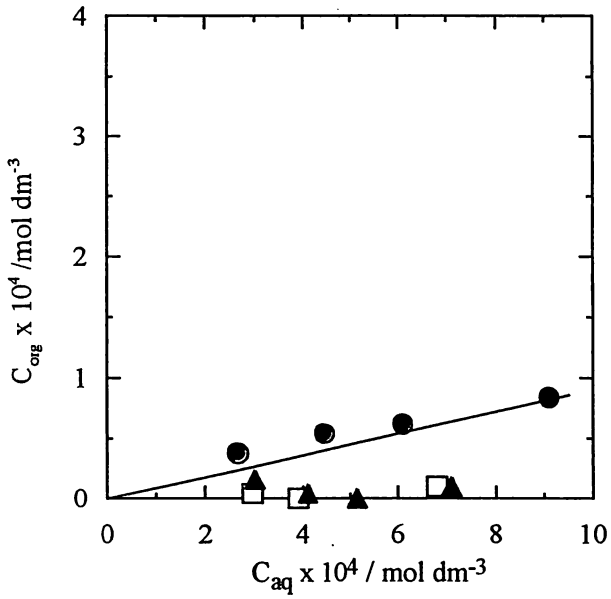


Fig.2 Extraction of catechols with chloroform alone.
Circle : catechol, triangle : resorcinol, square : hydroquinone.

Figure 3 shows the relationship between the concentrations of 3 types of catechols in the organic and aqueous phases after extraction with 5 mmol dm^{-3} of DEHAmidoPBA and DEA in chloroform. Although the extraction of resorcinol and hydroquinone is negligibly small with both reagents, catechol is significantly extracted with both reagents and the extraction with DEHAmidoPBA is much higher than that with DEA; that is, catechol having 2 hydroxyl groups in the α-position is significantly recognized by DEHAmidoPBA, the reagent containing boron. In the extraction of catechol with 5 mmol dm^{-3} of DEHAmidoPBA, the effect of pH was also examined over the pH range 3-8, from which it was found that the extraction is independent of pH.

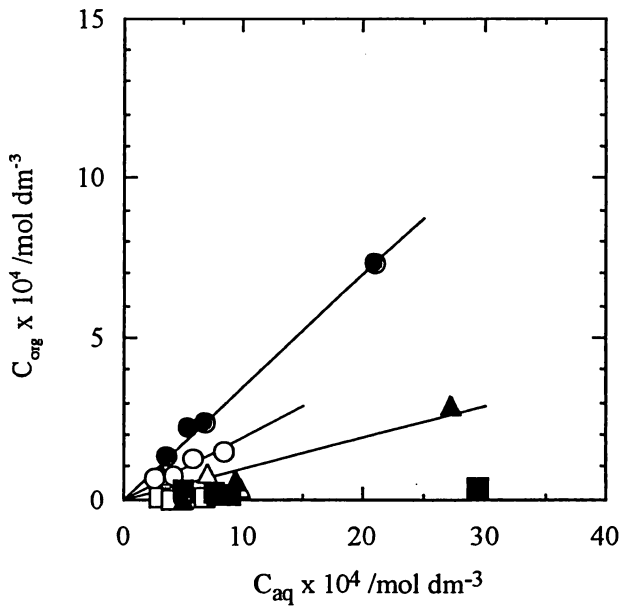


Fig.3 Extraction of catechols with DEHAmidoPBA and DEA in chloroform. Closed : DEHAmidoPBA, open : DEA, circle : catechol, triangle : resorcinol, square : hydroquinone.

Figure 4 shows the relationship between the concentrations of 3 types of catechols in the organic and aqueous phases after the extraction with 5 mmol dm^{-3} of DEHAminoPBA and DEA in hexane. In this case, only DEHAminoPBA selectively extracts catechol over other catechols.

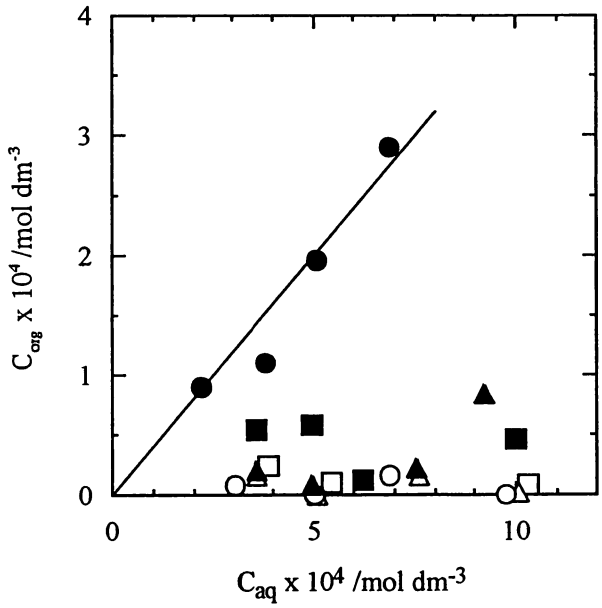


Fig.4 Extraction of catechols with DEHAminoPBA and DEA in hexane.
Closed : DEHAminoPBA, open : DEA, circle : catechol, triangle : resorcinol, square : hydroquinone.

Figure 5 shows the relationship between the concentrations of 3 types of catechols in the organic and aqueous phases after the extraction with 10 mmol dm^{-3} of TDBA in chloroform. Also in this case, only catechol is selectively extracted while resorcinol and hydroquinone are not appreciably extracted.

From the results of the solvent extraction tests described above, it is apparent that

all of the three boron-containing reagents can selectively extract or recognize catechol, a bishydroxybenzene with 2 hydroxyl groups at the α-position, from other catechols, which is considered to be ascribable to the formation of stable five-membered ring chelates as shown below.

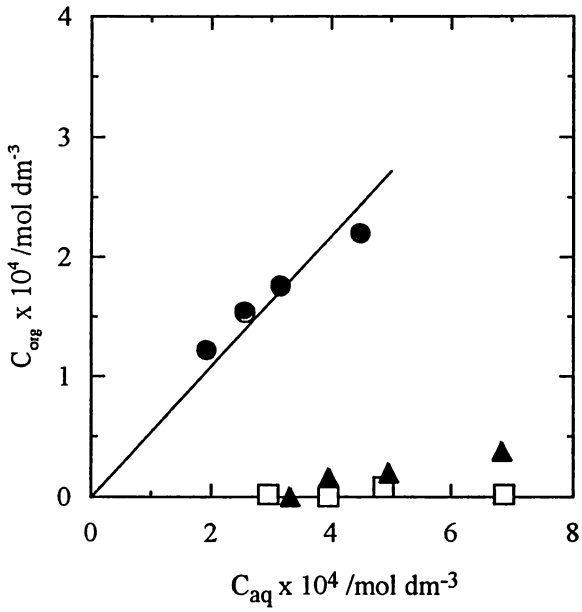
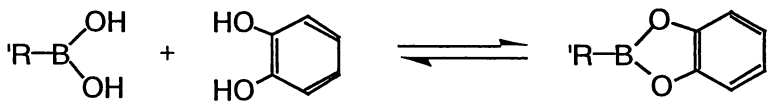


Fig.5 Extraction of catechols with TDBA in chloroform.

Circle : catechol, triangle : resorcinol, square : hydroquinone.



Although this reaction between boron and hydroxy groups is specific, it is reversible. From the results in Fig.3 and Fig.5 and talking the distribution of catechol into chloroform in Fig.2 into account, extraction equilibrium constants of catechol and resorcinol with

DEHAmidoPBA, DEA, and TDBA were estimated. The values are listed in Table 1. The extraction equilibrium constant of catechol with DEHAminoPBA in hexane was also estimated. The difference between the extraction ability between DEHAmidoPBA and DEA relates to the effect of boronic acid. The difference between DEHAminoPBA and DEA also relates to the effect of boronic acid. Thus, boron-containing extractants are very effective for the extraction of catechol from among other catechols.

Table 1 Extraction equilibrium constants, K_{ex} (mol dm^{-3}) for catechols with the extractants.

Extractant	DEHAmidoPBA	DEA	DEHAminoPBA	DEA	TDBA
Diluent	$CHCl_3$	$CHCl_3$	hexane	hexane	$CHCl_3$
catechol	1.03×10^{-3}	4.71×10^{-4}	1.45×10^{-3}	—	4.43×10^{-3}
resorcinol	3.73 x 10-5	—	—	—	—
hydorquinone	—	—	—	—	—

4. Conclusion

Three types of novel reagents containing a boronic acid functional group, 4-(di-2-ethylhexylamido)phenylboronic acid, 4-(di-2-ethylhexylaminomethyl)phenylboronic acid and 1-tetradecylboronic acid were synthesized. All of these reagents were found to have a high selectivity for catechol over resorcinol and hydroquinone, which was attributed to the formation of stable 5-membered chelates.

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