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Novel Synthesis of Perfluoroalkylated Phenylboronic Acid with Low pKa Using Bis(heptafluorobutyryl)peroxide as Perfluoroalkylation Reagent

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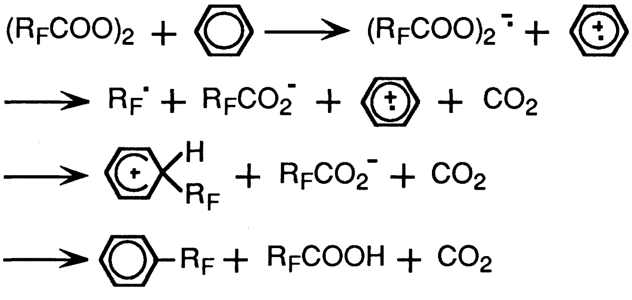
3-Acetamido-6-heptafluoropropylphenylboronic acid was synthesized by the perfluoroalkylation of 3-acetamidophenylboronic acid (pKa=8.3) with bis(heptafluorobutyryl)peroxide. The perfluoroalkylated phenylboronic acid thus prepared was determined to have a low pKa as 6.6 by potentiometric titration. Lowered pKa suggests that the product has an advantage for binding with polyols under physiological pH, opening a wide application in the field of biological as well as material sciences.

The formation of complexes between phenylboronic acid and polyols is well known and has been utilized for the fractionation of carbohydrates,1) separation of nucleotides,2) purification of peptides,3) and selective protection of carbohydrates for derivatization.4) Further, as we reported previously, glucose responsive insulin delivery system can be designed by utilizing the complex of boron-containing polymers and glucose.5,6)

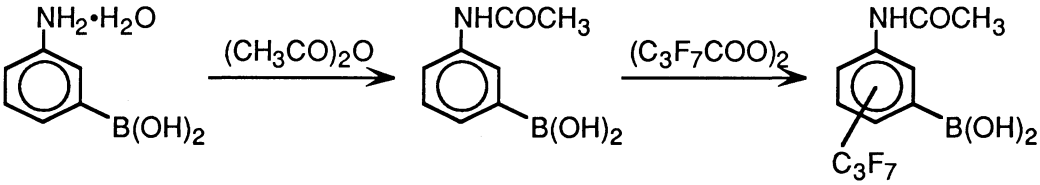
A major limitation of further use of this complex system under physiological pH is the relatively high ionization constant (pKa) of the phenylboronic acid moiety,5,6) because ionization is necessary for boronic acids to make stable complex with polyols in aqueous solution. The pKa of phenylboronic acids can be decreased by introducing electron withdrawing groups on the aromatic ring such as methylaminocarbonyl group,7) and nitro group.7,8) However, pKa of 4-(methylaminocarbonyl)phenylboronic acid is still high (pKa=8.0) for the use at physiological pH. Further, nitrophenylboronic acid derivatives requires laborious synthetic procedure, and are not suitable to use as a monomer in radical polymerization due to inhibitory effect of nitro groups on polymerization.

Perfluoroalkylated phenylboronic acid is promising candidate having sufficient low pKa as well as preferable structure as the starting compound to prepare vinyl monomer for the polymerization. To introduce perfluoroalkyl groups on the aromatic ring of phenylboronic acids, the perfluoroalkylation via electron-transfer process was carried out in this study using bis(perfluoroalkanoyl)peroxide as shown in Scheme 1.[9] This method was proved to be quite effective for the perfluoroalkylation of aromatic compounds, including methoxybenzene,[10] polystyrene,[11] furans, thiophenes, and pyridines.[12] Particularly, bis(heptafluorobutyryl)peroxide was used for introducing heptafluoropropyl group to phenylboronic acid as electron-withdrawing moiety to decrease pKa in this study.



Scheme 1.

The preparation procedure of 3-acetamido-heptafluoropropylphenylboronic acid was shown in Scheme 2. 3-Acetamidophenylboronic acid was prepared according to the literature.[13] Acetic anhydride (8.47×10^{-1} mol) was added to 3-aminophenylboronic acid monohydrate (1.29×10^{-1} mol) in 1,4-dioxane (300 ml), and then kept at 60 °C for 1 h. After the evaporation, the product was recrystallized from hot water (125 ml) to yield white crystals (80%), mp 273 °C.(lit[10] 275-276 °C) ; IR(KBr, cm^{-1}) : 1660,1540(-CO-NHR), 1310(B-O), 3350(NH), 3300,1530(B-OH), ^1H-NMR(DMSO-d_6, ppm) : 2.0(3H, CH_3), 7.2-7.8(4H, phenyl) 7.9(2H, OH), 9.8(1H, NH)



Scheme 2.

Bis(heptafluorobutyryl)peroxide (4.33×10^{-2} mol) in 1,1,2-trichloro-1,2,2-trifluoro-ethane (5%, NOF co.) was added to 3-acetamidophenylboronic acid (1.24×10^{-2} mol: 2.21g) in 1,1,1,3,3,3-hexafluoro-2-propanol (175 ml), and then kept at 0 °C for 13 days in nitrogen atmosphere. After the evaporation, 3.79 g of crude product was obtained. HPLC analysis suggested that the product is a mixture of the isomers. Major product was then isolated, and was determined the structure. The mixture (774 mg) was fractionated using ODS column (2.5 cmϕX25 cm) with 1%-acetic acid and N,N-dimethylformamide (6 ml/min.) as carrier solvent. The main fraction appeared in the elution volume ranging from 93 to 105 ml was collected (189 mg), and recrystallized from 18.9 ml of hot water. Quantity of the obtained crystal was 77 mg.

Characterization of fractionated product was then carried out, and the results are summarized in Table 1. IR result is consistent with the presence of perfluoroalkyl group in the molecule. The result of MASS reveals the number of substituent in aromatic ring. The value of 404 arises from the conjugate of the product with glycerin, [3-acetamido-heptafluoropropylphenylboronic acid + glycerin - $2H_2O$ + H$]^+$. The glycerin was

Table 1. Characterized chemical shifts of C3F7-acetylamido-phenylboronic acid

IR / cm^{-1}	νCF$_2$	1228
	νCF$_3$	1342
MASS (Fab) $[M+C_3H_8O_3-2H_2O+H]^+$		404
^{1}H-NMR / ppm	Acetyl	2.08(s,3H)
	Phenyl	7.48(d,1H) 7.63(s,1H) 7.79(d,1H)
	-OH	8.21(s,2H)
	Amide	10.20(s,1H)
^{13}C-NMR / ppm	Phenyl	117.81 121.31 127.51
pKa		6.6

Table 2. Calculated results of 13C-NMR on heptafluoropropyl-acetylamidophenylboronic acid

Position \ Substituted position	4	6
2	114.57±17.05(s)	114.57±17.05(s)
4	-	117.91±1.16(d)
5	129.10±0.75(d)	129.15±0.60(d)
6	133.64±1.38(d)	-

This value is represented in ppm.
( ): ^{1}H-^{1}H couplings are indicated in parenthesis on bound proton.

added as a matrix compound for the measurement of fab MASS, and seems to make complex with phenylboronic acid moiety in the compound. This complexation enabled perfluoroalkylated phenylboronic acid to vaporize, because hydrogen bonding due to boronic acid moiety was diminished through the complexation. The result of MASS indicates that this product is mono substituted isomer. ^{1}H-NMR result reflects the isomeric structure of 3-acetamidoheptafluoropropylphenylboronic acid. The results of doublet-singlet-doublet at phenyl protons suggest that this product has substituted at 4 th or 6 th position in phenyl ring.

In order to determine the substituted position, the result of ^{13}C-NMR (Table 1) was compared with calculated chemical-shift by the data generation package "SPECAL" in SPECINFO (STN-International). This package uses a substructure code developed to characterize the spherical environment of individual atoms.$^{14)}$ Table 2 shows the calculation results of ^{13}C-NMR on two kinds of 3-acetamidohepta-fluoropropylphenylboronic acids substituted at 4th or 6th position in phenyl ring.

^{1}H-^{13}C COSY spectrum indicates the couplings of 7.48(d)-127.51, 7.63(s)-121.31, and 77.9(d)-117.81 on the phenyl ring. Three measured chemical-shifts were compared with the calculated values in Table 2, especially for the carbon atoms having proton with doublet-^{1}H-NMR peak. The chemical-shifts of the product considerably fits to calculated result of 6th position isomer of 3-acetamido-6-heptafluoropropylphenylboronic acid.

The potentiometric determination of pKa value was accomplished by titration of 3-acetamido-6-heptafluoropropylphenylboronic acid in H_2O by standardized 0.01N-HCl solution. The pKa value was determined from the inflection points of the titration. 3-acetamido-6-heptafluoropropylphenylboronic acid was shown to have a pKa of 6.6. This value is considerably lower than pKa=8.3 of 3-acetamidophenylboronic acid.$^{8)}$ Percentage of tetrahedral-formed phenylboronic acid (ionized form) was calculated to be 86% for 3-acetamido-6-heptafluoropropylphenylboronic acid at physiological pH=7.4. This is in sharp contrast to the value for 3-acetamidophenylboronic acid, which was calculated to have the ionization degree of only 11%.

The increased percentage of tetrahedral form suggests that the phenylboronic acid group in the compound has high ability to make stable complex with polyol even under physiological pH. We suggest that the perfluoroalkylated phenylboronic acid is a promising starting material for preparing separation system of polyols, including nucleotides, from biological fluid, for the protection of glycoproteins and nucleotides during their chemical modification, and especially for designing controlled insulin release system to be useful under physiological pH.

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