

Thermodynamic and structural study of complexation of phenylboronic acid with salicylhydroxamic acid and related ligands

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Stability constants of boronate complexes with a highly efficient bioconjugation ligand salicylhydroxamic acid, its derivatives and some structurally related compounds were determined by potentiometric and spectroscopic titrations at variable pH allowing one to obtain detailed stability – pH profiles and to identify the optimum pH for complexation with each ligand. The N,O-binding of salicylhydroxamic acid via condensation of boronic acid with phenolic OH and hydroxamic NH groups was established by crystal structure determination of isolated complexes with phenylboronic and 4-nitrophenylboronic acids. Although this type of binding is impossible for N-methylated salicylhydroxamic acid it still forms stable boronate complexes supposedly involving unusual 7-membered –O-B-O– cycle supported by ¹H NMR studies. Hydroxamic acids lacking *ortho*-OH group and salicyloyl hydrazide form less stable boronate complexes, which nevertheless possess stabilities similar to those of catecholate complexes and may be useful for conjugation applications. In contrast to other ligands, which form tetrahedral anionic complexes, salicylamidoxime forms tetrahedral, but neutral boronate complex with high stability in weakly acid solutions. The highest affinity in neutral and acid solutions surpassing that of salicylhydroxamic acid is observed with 2,6-dihydroxybenzhydroxamic acid ($K_{\text{obs}} = 5.2 \times 10^4$ at pH 7.4). Fairly stable mono- and bisboronate complexes are formed with 2,5-dihydroxy-1,4-benzdihydroxamic acid, which also possesses intense fluorescence and may serve as a boronic acid sensor with detection limit 4 μM . Results presented in this study provide quantitative basis for rational applications of hydroxamic acid derivatives in bioconjugation and sensing.

KEYWORDS

boronic acid, complexation, crystal structure, hydroxamic acid, stability constant

1 | INTRODUCTION

Complex formation with boronic acids represents one of important types of bioorthogonal chemical reactions often employed in bioconjugation chemistry.^[1] The most

common type of complexation of boronic acids in water is formation of diol esters which finds applications in molecular recognition of sugars and other polyols^[2] as well as in self-assembly of pH and/or sugar responsive supramolecular structures.^[3–6] When fragments of