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FORMATION OF HETERO-BOROXINES: DYNAMIC COMBINATORIAL LIBRARIES GENERATED THROUGH TRIMERIZATION OF PAIRS OF ARYLBORONIC ACIDS

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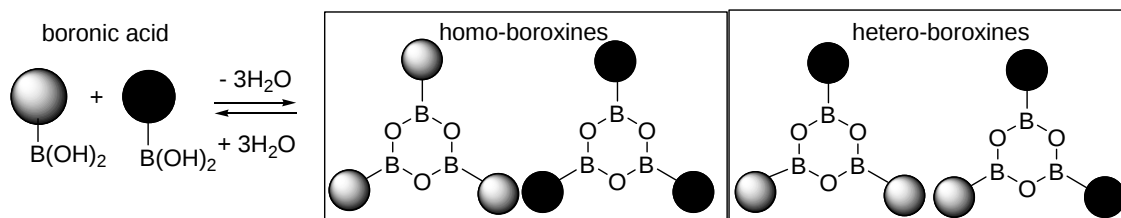
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Abstract – Condensation of pairs of arylboronic acids provided homo- and hetero-boroxines in solution as evidenced from NMR spectra, and those boroxines were detected in the gas phase by GC-MS spectrometry. Equilibrium constants for the formation of these boroxines in solution were obtained through integration of pertinent signals in the NMR spectra of the mixtures of boronic acids.

Boroxines, cyclic anhydrides of boronic acids, are six-membered inorganic heterocycles that have been used as flame retardant materials,¹ dopants that enhance lithium ion transfer in polymer electrolytes,² nonlinear optical materials,³ and agents that expand the functional and structural complexity of polymeric materials.⁴ Two attractive features of boroxines are their C_3 -symmetric tripodal structures⁵ and Lewis acidity,⁶ which provides the additional possibility of functionalizing the boroxine core through noncovalent interactions. Recently, we⁷ and the Kua group⁸ reported the thermodynamics of formation of boroxines from boronic acids. The equilibrium constants between the boronic acids and the boroxines in the presence of water have been measured using NMR spectroscopy, and a computational study has provided details of their thermodynamic and kinetic behavior. Those reports, however, discussed only homo-boroxines assembled from single monomeric boronic acids. In this paper, we describe the formation and stabilities of hetero-arylboroxines (Scheme 1).

We employed several symmetrical arylboronic acids (**1–5**) to determine whether it would be easy to analyze their resulting hetero- and homo-boroxines using ^1H NMR spectroscopy (Figure 1). The rates of formation and hydrolysis of the boroxines were slow on the NMR spectroscopic timescale at room temperature, as reported previously.⁷ The ^1H NMR spectra (CDCl_3) of mixtures of pairs of these boronic

acids in the presence of water provided evidence for formation of their corresponding two homo- and two hetero-boroxines, respectively. For example, the ^1H NMR spectrum of a mixture of **1** and **2** (Figure 2) displays an array of well-defined signals.



Scheme 1.

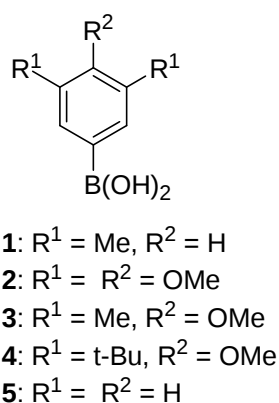


Figure 1.

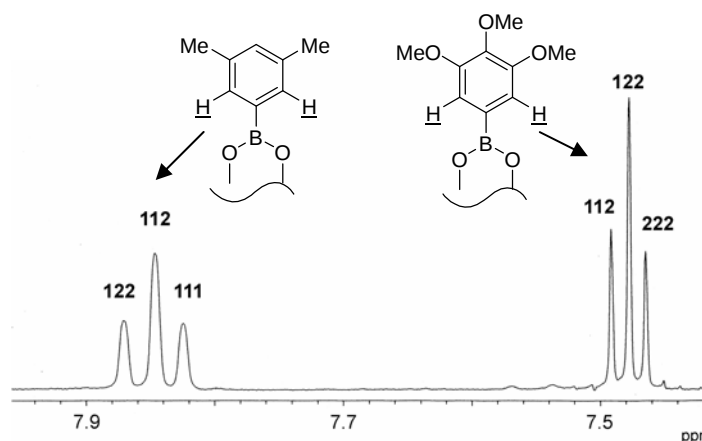


Figure 2. Partial ^1H NMR spectrum (500 MHz, CDCl₃, 25 °C) of a mixture of boronic acids **1** and **2**.

We calculated the equilibrium constants (K_{eq}) for the formation of the four boroxines through integration of the signals of the seven species (two boronic acids, two homo-boroxines, two hetero-boroxines, and water) present in the ^1H NMR spectra (Table 1). In the same manner, we performed variable-temperature NMR spectroscopy experiments to obtain thermodynamic information relating to these equilibria. The van't Hoff plot for each equilibrium yielded a straight line, from which we determined the enthalpic and entropic parameters. A previous report⁷ suggested that the presence of an electron-donating group in the para position of the phenyl ring increases the stability of the boroxine derivative toward hydrolysis; computational studies supported this empirical finding.⁸ Our results agree with this concept.⁹ Another significant observation is that, in all cases, entropically driven forces promoted the formation of boroxine. The process involving construction of rigid boroxine would appear to be entropically unfavorable, however, it includes the release to the bulk solvent of three free water molecules from boronic acid.⁷ In consideration of the four possible boroxines (**AAA**, **AAB**, **ABB**, **BBB**) formed from a binary mixture of boronic acids **A** and **B**, we would expect a statistical distribution of 1:3:3:1 for a mixture of equally

stable members. The statistical values reflect the experimental results, K_{eq} values for the hetero-boroxines is generally larger than those for homo-boroxines.¹⁰ Additionally, the hetero-boroxines possessed larger values of K_{eq} when they incorporated monomeric boronic acids that formed homo-boroxines having larger values of K_{eq} .

Table 1. Thermodynamic parameters for the formation of homo- and hetero-boroxines.^{a,b,c}

boronic acid A	boronic acid B	boroxine	K_{eq}^d mol/l	ΔG^d kJ/mol	ΔH kJ/mol	ΔS J/K·mol
1 $R^1 = \text{Me}$ $R^2 = \text{H}$	2 $R^1 = R^2 = \text{OMe}$	111	0.14 ± 0.01	4.9 ± 0.2	22 ± 2	58 ± 6
		112	0.42 ± 0.03	2.2 ± 0.2	20 ± 2	61 ± 4
		122	0.37 ± 0.04	2.5 ± 0.3	20 ± 2	60 ± 4
		222	0.11 ± 0.02	5.5 ± 0.4	27 ± 3	74 ± 9
3 $R^1 = \text{Me}$ $R^2 = \text{OMe}$	1 $R^1 = \text{Me}$ $R^2 = \text{H}$	333	0.46 ± 0.08	1.9 ± 0.5	11 ± 6	31 ± 19
		331	0.86 ± 0.04	0.4 ± 0.1	12 ± 4	40 ± 14
		311	0.60 ± 0.00	1.3 ± 0.1	14 ± 5	42 ± 15
		111	0.11 ± 0.03	5.5 ± 0.7	18 ± 2	41 ± 4
4 $R^1 = t\text{-Bu}$ $R^2 = \text{OMe}$	3 $R^1 = \text{Me}$ $R^2 = \text{OMe}$	444	0.52 ± 0.04	1.6 ± 0.2	13 ± 1	39 ± 4
		443	0.82 ± 0.06	0.5 ± 0.2	12 ± 0	38 ± 1
		433	0.61 ± 0.00	1.2 ± 0.0	12 ± 2	35 ± 5
		333	0.34 ± 0.01	2.7 ± 0.1	14 ± 3	38 ± 9
4 $R^1 = t\text{-Bu}$ $R^2 = \text{OMe}$	1 $R^1 = \text{Me}$ $R^2 = \text{H}$	444	0.69 ± 0.06	0.9 ± 0.2	13 ± 1	41 ± 3
		441	0.76 ± 0.03	0.7 ± 0.1	17 ± 1	55 ± 3
		411	0.43 ± 0.01	2.1 ± 0.1	18 ± 1	55 ± 1
		111	0.18 ± 0.01	4.2 ± 0.2	16 ± 1	38 ± 4
3 $R^1 = \text{Me}$ $R^2 = \text{OMe}$	2 $R^1 = R^2 = \text{OMe}$	333	0.29 ± 0.02	3.0 ± 0.2	17 ± 1	46 ± 3
		332	0.66 ± 0.05	1.0 ± 0.2	16 ± 2	49 ± 4
		322	0.47 ± 0.07	1.9 ± 0.4	20 ± 2	61 ± 4
		222	0.09 ± 0.03	6.0 ± 0.9	31 ± 6	84 ± 18
4 $R^1 = t\text{-Bu}$ $R^2 = \text{OMe}$	2 $R^1 = R^2 = \text{OMe}$	444	0.70 ± 0.08	0.9 ± 0.3	11 ± 2	33 ± 8
		442	1.35 ± 0.12	-0.7 ± 0.2	13 ± 2	47 ± 6
		422	0.78 ± 0.01	0.6 ± 0.1	17 ± 2	54 ± 8
		222	0.15 ± 0.01	4.7 ± 0.2	26 ± 2	71 ± 6

^a All experiments were performed more than twice, and the average is shown in Table 1.

^b Concentration data were obtained from integrations of the appropriate signals for boronic acids, boroxines, and water, compared with standard (hydroquinone dimethyl ether) in the ¹H NMR spectra recorded in CDCl₃.

^c $K_{eq} = [\text{boroxine}] [\text{H}_2\text{O}]^3 / [\text{boronic acid}]^3$

^d at 25°C

GC-MS experiments showed the existence of four possible boroxines from the boronic acids **1** and **5** in the gas phase. The GC spectrum of this mixture in chloroform displayed four abundant peaks (Figure 3a), the mass spectra of which provided signals for the molecular ions [M^+] of the homo-boroxine **555**, the hetero-boroxine **155**, the hetero-boroxine **115**, and the homo-boroxine **111**, respectively, at m/z 312, 340, 368, and 396, respectively (Figures 3b–e). No or very small amount of signals based on other boroxines in the MS spectra of hetero-boroxines showed that the intermolecular exchange of monomeric units in the boroxines hardly proceeded under the GC-MS conditions.

In summary, using ^1H NMR spectroscopy and GC-MS techniques, we have demonstrated that pairs of boronic acids form their two possible homo- and hetero-boroxine pairs in solution and in the gas phase. Dynamic combinatorial chemistry, which relies on reversible covalent processes for the spontaneous and continuous generation of dynamic combinatorial libraries, has garnered much attention recently.¹¹ Our observations described herein indicate that it is possible to form all of the expected boroxines from solutions of two different boronic acids at equilibrium. Because the condensation reactions that lead to the formation of the boroxines occur under mild conditions, these compounds could be useful components of dynamic combinatorial libraries.

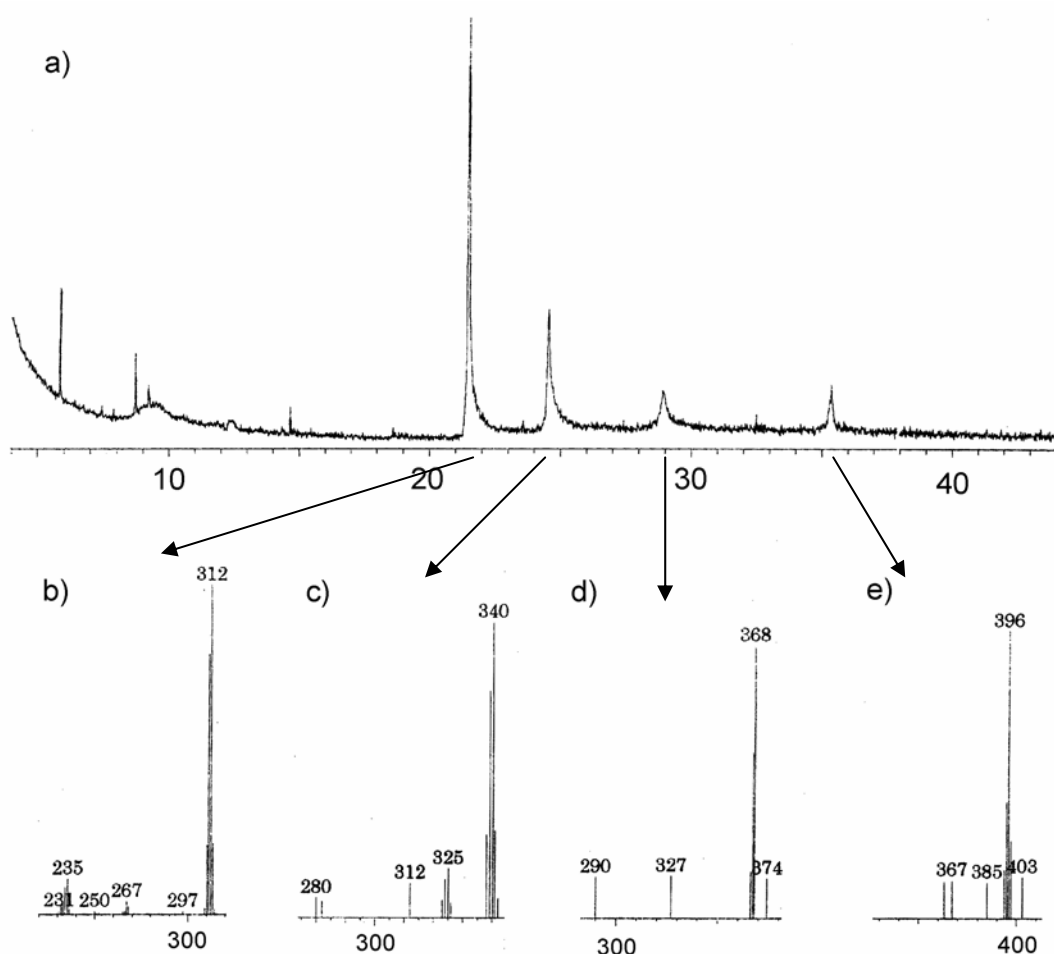


Figure 3. GC-MS spectra obtained from a mixture of boronic acids **1** and **5**. (a) Gas chromatogram and (b–e) partial MS spectra of (b) 555, (c) 155, (d) 115, and (e) 111.

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