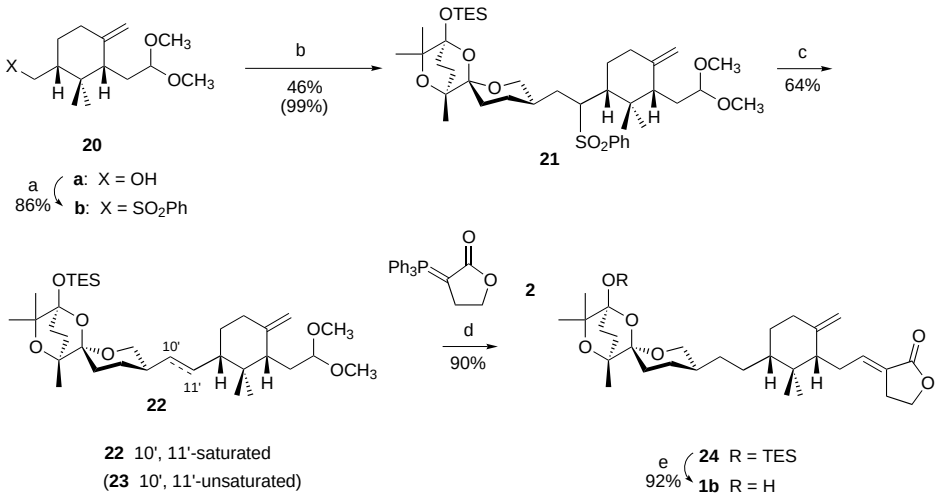

Scheme 4. a) $(C_4H_9)_3P$, PhSSPh, PhH, RT then TPAP, NMO, 4-Å MS, CH_3CN, 0 °C; b) n-C_4H_9Li, THF, HMPA, **19d**, $-55 \rightarrow -30$ °C; c) 5% Na(Hg), NaH_2PO_4, CH_3OH, -15 °C; d) CF_3CO_2H, THF, H_2O, RT, then **2** CH_2Cl_2, RT; e) TBAF, HOAc, THF, RT. HMPA = hexamethyl phosphoramide. Yields in parentheses are based upon recovered starting material.

Alkylation of a sulfone-stabilized anion was chosen for the coupling of fragments **3** and **4**. The sulfone **20b** was prepared from the corresponding alcohol **20a** in 86% yield by sulfide displacement followed by oxidation[8] (Scheme 4). The alkylation of sulfone **20b** with iodide **19d** proceeded nearly quantitatively at 50% conversion.

Reductive desulfonylation of **21** with sodium amalgam[9] gave **22** accompanied, surprisingly, by some elimination product **23**. That the alkene **23** did not form by base-catalyzed elimination is suggested by the absence of any dependence on the amount of added buffer nor on varying the reductant to samarium diiodide.[10, 11] The completion of the synthesis proceeded straightforwardly as outlined (Scheme 4). Olefination of the aldehyde liberated from the acetal **22** with the stabilized Wittig reagent **2**[12] gave a 13:1 ratio of the E:Z alkenes. The lower field shift ($\delta = 6.70$) of the new olefinic hydrogen of the major isomer compared to the minor one ($\delta = 6.19$) establishes the former as the E alkene. Desilylation then delivers synthetic saponaceolide B (**1b**, $[\alpha]_D^{22} = +14.4$, $c = 1.54$ in CH_2Cl_2), whose spectral data agrees well with those recorded for the natural product.[1] The success of this synthesis derived from its access to a stereodefined cyclohexyl unit, which in turn is prepared by the palladium-catalyzed cycloisomerization of enynes or the Heck protocol.[13] The convergent strategy should also provide access to other members of the saponaceolide family as well their analogues. The strategy outlined also provides opportunities to provide other natural products emanating from the cyclohexyl core **3**.

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Teaching Old Indicators New Tricks: A Colorimetric Chemosensing Ensemble for Tartrate/Malate in Beverages**

John J. Lavigne and Eric V. Anslyn*

The development of general methods for the colorimetric analysis of small and medium-sized analytes in solution is highly desirable since visual inspection yields immediate qualitative information, while absorption spectroscopy gives quantitative information. Many colorimetric assays exist, but most often they deal with the analysis of pH,[1] simple cations[2] and anions,[3] and radicals.[4] The majority of these sensors have the chromophore covalently attached to the recognition element. Upon binding of the analyte the electronic transitions of the chromophore are perturbed. In contrast, many colorimetric assays for large biological mole-

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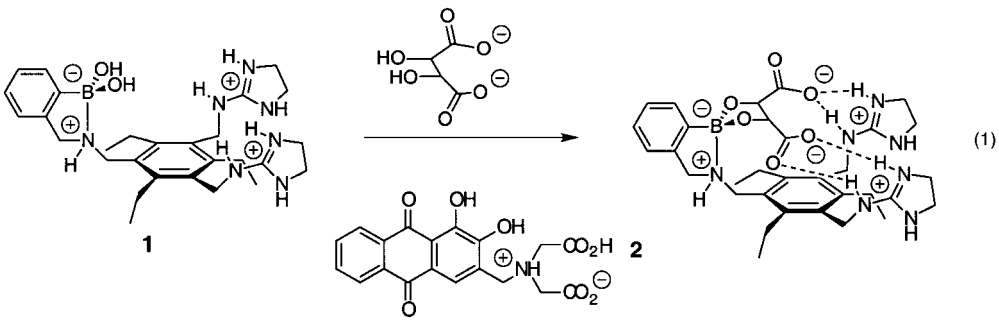
cules are known. These screens most often employ antibodies, as in common pregnancy tests,[5] or biotin–avidin-based sandwich assays. However, another alternative that is amenable to the creation of a colorimetric method, and still used almost exclusively in biological systems, involves the competition of an indicator with the desired analyte.[6] For example, upon exposure of an immobilized antibody saturated with a tagged antigen to analyte, a competition for the antibody binding site takes place between the tagged antigen and the target analyte, which results in a signal modulation.

We have recently been exploring fluorescence competition assays employing synthetic receptors.[7] Fluorescence is useful for the analysis of analytes that are present at very low concentrations. However, the concentrations of many common analytes in beverages, bodily fluids, and environmental samples are quite amenable to analysis by absorption spectroscopy. Hence, given the advantage of having a colorimetric assay we set out to develop a general method for creating colorimetric assays from synthetic receptors. Herein we report a specific example: the analysis of tartrate in beverages.

Tartrate is a common natural product present in wines and other grape-derived beverages. The structure of tartrate makes it quite attractive for complexation by a synthetic receptor since it is relatively small, while still possessing several functional groups (alcohols and carboxyl groups) for binding interactions. On the basis of the previous use of boronic acids to bind 1,2- and 1,3-diols,[8] and guanidinium groups imbedded in aminoimidazoline groups for binding carboxylates,[9] we designed synthetic receptor **1** for tartrate [Eq. (1)].[10] Compound **1** features a single boronic acid and two guanidinium groups preorganized to converge and create a cavity of the correct dimensions for tartrate. The preorganization comes from the use of a hexasubstituted benzene ring, where it has been shown that the steric bulk forces the alternating substituents to opposite sides of the benzene spacer.[11]



(1)

There is a significant amount of prior precedence for the use of an aminomethyl moiety in the position *ortho* to a boronic acid in a sensor. All of these use a tertiary amine that is involved in the signal transduction mechanism, usually by quenching of the signal by photoinduced electron transfer (PET)[12] or internal charge transfer (ICT).[13] The current system utilizes a secondary amine solely for linking and restricting the degrees of freedom of the boronic acid group.[14] Studies of other secondary amines coordinated to boronic acids suggest a zwitterionic complex containing tetracoordinate boron and nitrogen atoms.[15] The strength of the N–B interaction is approximately 19 kcal mol^{-1}.[15a] The geometry of the boron atom was determined from a ^{11}B NMR spectrum of **1**. Under the assay conditions (see Experimental Section), the spectrum shows one peak at $\delta = 12.8$ (referenced to BF_3Et_2O in toluene at $\delta = 0$), which is indicative of a tetrahedral boron atom.[16]

A pH indicator with a chromophore possessing the same functionalities as tartrate was chosen for use in a competition assay. Importantly, the choice of indicator was guided by the expectation that complexation by the receptor would result in a color change of the indicator. This effect is afforded by a change in the "protonation state" (for this analysis we consider the boron atom to be acting like a proton) when the indicator is either bound to the receptor or free in solution at a constant pH. We chose alizarin complexone (**2**) for the analysis of tartrate [Eq. (1)] since it also possesses a 1,2-diol and two carboxylate groups. This indicator has been previously used to signal a change in pH[17] as well as the presence of lanthanide,[17] and fluoride ions .[18] The functional groups are not arranged in the same manner as with tartrate, and hence a lower affinity between **1** and **2** was anticipated. We predicted that the binding between **1** and **2** would significantly shift the "protonation state" of the phenols as a result of the formation of a boronate ester as a result of reaction with to the boronic acid. Indeed, the color changed from burgundy to yellow/orange (Figure 1 A) upon addition of **1** to a solution of **2** (0.1 mM) in a water/methanol mixture (25 vol% water; pH 7.3, buffered with 10 mM HEPES). By following the absorption at 450 nm and fitting the data to a 1:1 binding algorithm[19] a binding constant of $2.7 \times 10^4\,\text{M}^{-1}$ was obtained.

As expected, the addition of stock solutions of L-tartrate to an ensemble of **1** and **2** (see Experimental section; this solution is referred to as the sensing ensemble) resulted in a change from yellow/orange back to burgundy (Figure 1 B). We analyzed for tartrate as well as several other possible competing analytes with structures similar to tartrate, including: ascorbate, L-malate, succinate, lactate, and sugars, using this colorimetric assay (Figure 2). A binding constant of $5.5 \times 10^4\,\text{M}^{-1}$ was calculated for **1** and tartrate using algorithms for competitive equilibria.[19] In comparison, a binding constant of $150\,\text{M}^{-1}$ between **1** and glucose was measured by UV/Vis spectroscopy; this value is in the range found for a single boronic acid and a sugar.[12b] We also found that succinate binds to **1** with a binding constant of $350\,\text{M}^{-1}$. Furthermore, a monohydroxy carboxylate such as lactic acid only had a binding constant of $500\,\text{M}^{-1}$ with **1**. With the exception of malate (K_a with **1** is $4.8 \times 10^4\,\text{M}^{-1}$) we find excellent selectivity for tartrate. Hence, good cooperativity exists between the boronic acid and the two guanidinium

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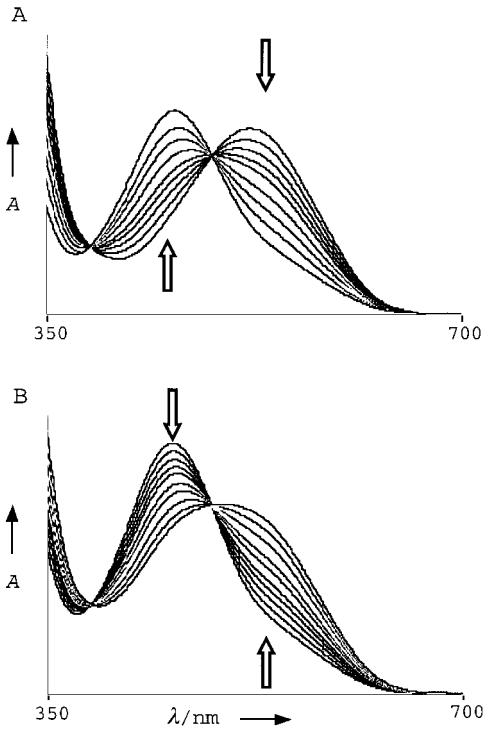

Figure 1. UV/Vis spectra of **2**. A) Addition of **1** to a constant concentration of **2** (180 μM) results in an increase in the absorbance at 450 nm with a decrease in absorbance at 525 nm. B) Addition of tartrate to a solution containing both **1** and **2** (180 μM each) at a constant concentration causes a decrease in the absorbance at 450 nm and an increase in the absorbance at 525 nm.

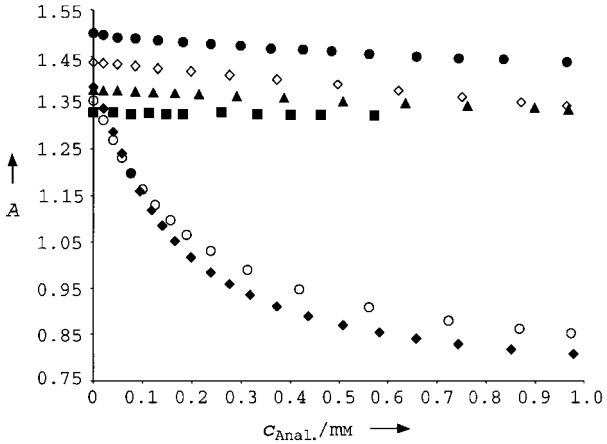

Figure 2. Calibration curves at 450 nm used for the sensor assay. Addition of tartrate (◆), malate (○), ascorbate (◇), lactate (◆), succinate (▲), and glucose (■). $c_{Anal.}$ = concentration of the analyte.

groups of **1** for the complexation of the hydroxyl and carboxylate moieties of tartrate.

For final proof of principle the calibration curves generated for tartrate and malate (Figure 2) were used to evaluate various solutions. The addition of microliter quantities of several grape-derived beverages to the sensing ensemble gave the concentrations of tartrate/malate present (Table 1). An NMR assay for the total tartrate/malate concentration was used as a control. In all cases very good agreement (less than 10% difference) between the two methods was obtained. This suggests that the sensing ensemble is able to quantitate tartrate/malate in the presence of large concentrations of sugars, electrolytes, pectins, and tannins.

Table 1. Concentration of tartaric and malic acids [mM] in different solutions as determined by different methods.

	Gravimetric	NMR	UV/Vis (**1** + **2**)
tartaric acid model solution	50	51.2	50.2
calibration solution	50	–	47.9
Ernest & Julio Gallo Sauvignon Blanc	–	35.6	32.9
Ste. Genevieve Chardonnay	–	34.1	36.3
Henri Marchant Spumante	–	26.5	24.9
Talus Merlot	–	19.5	20.3
Santa Cruz organic white grape juice	–	43.6	42.3
Welch's grape juice	–	69.4	71.3

In summary, a colorimetric assay for tartrate using a synthetic receptor has been created. In this assay a common pH indicator that has the same or similar functionalities to that of the analyte of interest has been used. Since the receptor is most complementary to the analyte there is a lower relative affinity for the indicator, which leads to the facile displacement of the indicator from the receptor upon addition of the analyte and a color change of the indicator occurs. We are currently exploring this approach for the analysis of many other analytes in liquids.

Experimental Section

1: 1-aminomethyl-2,4,6-triethyl-3,5-(*N*-(imidazoline-2-yl-aminomethyl)benzene (300 mg, 0.53 mmol)[20] was mixed with (2-formylphenyl)boronic acid (87.6 mg, 0.58 mmol) in anhydrous methanol to which was added distilled triethylamine (360 μL, 2.65 mmol) and activated 3-Å molecular sieves. The solution was stirred at 25 °C for 3 h. Sodium borohydride (20.2 mg, 0.53 mmol) was then added to the solution and stirred for an additional hour. The solution was filtered through a pad of celite to remove the sieves and the solvent removed by rotary evaporation. The resulting residue was placed under reduced pressure (6 Torr) for two days to remove the trimethylborate. This residue was then dissolved in water and filtered through a pad of celite to remove the reduced aldehyde. The water was lyophilized to yield a fluffy white solid (366 mg, 99%). M.p. 197 °C (decomp); ^{1}H NMR (300 MHz, CD_3OD, 25 °C): $\delta = 1.12$ (t, 6H; CH_3), 1.23 (t, 3H; CH_3), 1.81 (s, 9H; CH_3), 2.74 (q, 2H; CH_2), 2.82 (q, 4H; CH_2), 3.75 (s, 8H; CH_2), 3.97 (s, 2H; CH_2), 4.11 (s, 2H; CH_2), 4.43 (s, 4H; CH_2), 7.11 (d, 1H; Ph), 7.15–7.23 (m, 2H; Ph), 7.49 (d, 1H; Ph); ^{13}C NMR (75 MHz, CD_3OD, 25 °C): $\delta = 16.4$, 16.6, 23.1, 24.1, 42.0, 44.1, 53.5, 116.2, 127.9, 128.4, 130.8, 131.4, 146.7, 161.2, 162.8, 163.2, 178.8; ^{11}B NMR (160 MHz, CD_3OD, 25 °C): $\delta = 8.2$; HR-MS (FAB (gly), as the glycerol boronate ester): *m*/*z*: found: 576.3839; calcd for $C_{31}H_{47}BN_7O_3$: 576.3833 [M^++1].

UV/Vis determination of tartrate/malate: HEPES buffer (10 mM) at pH 7.35, **1** (180 μM), alizarin complexone (180 μM) in 25% water in methanol. Sample preparation involved adjusting the pH of beverage (5 mL) with aqueous sodium hydroxide and diluting to 10 mL with water. An aliquot of this dilute wine solution (40 μL) was added to the sensing ensemble (960 μL; to maintain a constant indicator and host concentration). A portion of this solution (5– 50 μL) was then added to the sensing ensemble (1 mL). The average of four scans was used to determine one value.

NMR determination of tartrate/malate: Beverage (50 mL) was adjusted to pH 7.35 with aqueous sodium hydroxide and the water removed by lyophilization. The residue was then dissolved in D_2O (5 mL) and the volume brought to 10 mL with D_2O. The internal reference solution was made by dissolving dichloroacetic acid(0.5 mL) in D_2O, the pH brought to 7.35 with sodium deuteroxide, and the volume brought to 10 mL. D_2O (800 μL) was combined with dichloroacetic acid solution (100 μL) in an

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NMR tube and wine solution (100 and 300 μL) added. The area of the integral for dichloroacetic acid was normalized to the areas from malate and tartrate and the concentrations calculated.

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New Efficient Multicomponent Reactions with C–C Coupling for Combinatorial Application in Liquid and on Solid Phase**

Armin de Meijere,* Hanno Nüske, Mazen Es-Sayed, Thomas Labahn, Maarten Schroen, and Stefan Bräse*

Dedicated to Dr. Pol Bamelis on the occasion of his 60th birthday

Elegance in chemical synthesis is reflected in the art of finding simple ways to construct complex structures.[1] In the age of combinatorial chemistry,[2] multicomponent and domino reactions[3] are of special importance. This is especially true for liquid-phase combinatorial chemistry,[4] in which the usually required and always relatively time-consuming purification often limits the practical sequences to a few steps.[5] In the continuing development of classic multicomponent reactions, for example those developed by Ugi,[6a] Biginelli,[6b] and Mannich,[6c] the preferential formation of heteroatom – carbon bonds is prominent. We were recently able to extend the repertoire of less common cascade reactions solely leading to

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