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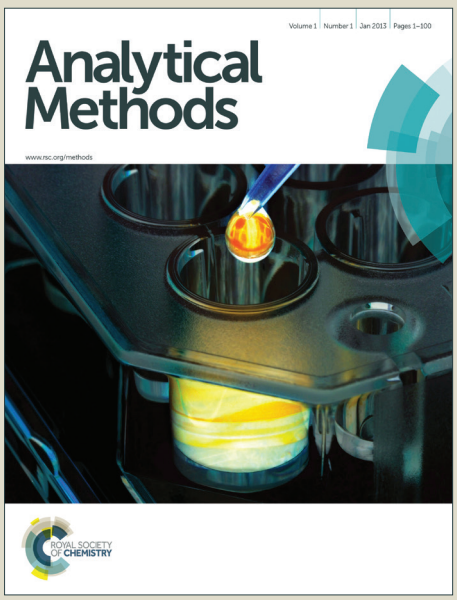

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Potentiometric Determination of Acid Dissociation Constants of Novel Biaryl Monomers

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The acid dissociation constants (pK_as) of a number of novel polymerisable vinyl biaryl compounds, 4-(4'-ethenylphenyl)-pyridine (**M1**), 4'-ethenyl-(1,1'-biphenyl)-4-ol (**M2**) 4'-ethenyl-N,N-dimethyl-(1,1'-biphenyl)-3-amine (**M3**), 4'-ethenyl-(1,1'-biphenyl)-4-methanol (**M4**), 4'-ethenyl-N,N-dimethyl-(1,1'-biphenyl)-4-amine (**M5**), 4'-ethenyl-(1,1'-biphenyl)-4-carboxylic acid (**M6**), 4'-ethenyl-4-hydroxy-5-methyl-(1,1'-biphenyl)-3-carboxaldehyde (**M7**) were determined in a mixed solvent (THF-water) potentiometric titration at 25°C and subsequent extrapolation to pure water via the Yasuda-Shedlovsky method. The acidity and basicity of the compounds in THF-water mixtures was observed to decrease with increasing THF fraction and is attributed to the corresponding decrease in the dielectric constant of the solution. To the best of our knowledge, this is the first reported study of pK_a values undertaken for this class of compounds. The biaryls, **M1**-**M7**, were prepared by microwave-assisted Suzuki cross coupling of 4-vinylphenyl boronic acid with the appropriate aryl bromide and were custom designed for use as functional monomers in the synthesis of molecularly imprinted polymers.

Introduction

Biaryls are common backbones found in both biologically active drug candidate compounds,[1-4] and natural products.[5-7] They also serve as building blocks for the synthesis of complex, high molecular weight materials which form the basis of nanomaterials, sensing devices and catalysts.[6,8]

The novel polymerisable biaryls **M1**-**M7** investigated in this study were previously prepared by Suzuki cross coupling of 4-vinylphenyl boronic acid with a range of substituted aryl bromides utilising microwave irradiation (Figure 1).[9] The biaryl units were designed and synthesised as functional monomers in the synthesis of molecularly imprinted polymers (MIPs) for a range of target species.[10] Functional monomer selection in MIP synthesis is critical for establishing strong non-covalent template (T) - functional monomer (FM) interactions in solution. These interactions directly determine the stability and stoichiometry of the T-FM cluster in solution during polymer formation and impact on the fidelity of template-selective cavities formed in the resulting polymer matrix (the template being removed from the cavity by extraction post-polymerisation). MIP rebinding is akin to enzyme-substrate recognition in biological systems, with template selectivity achieved via the presence of the now frozen and proximally located FM units within the cavity. The functional groups present on the biaryl monomers possess characteristics (e.g. acidity, basicity, hydrogen bonding capability) that make it possible to imprint a range of pH- sensitive target molecules. To have a full understanding of the exact nature of potential interactions under varying pH conditions, knowledge of the acid dissociation constants (pK_as) of the monomers is essential.

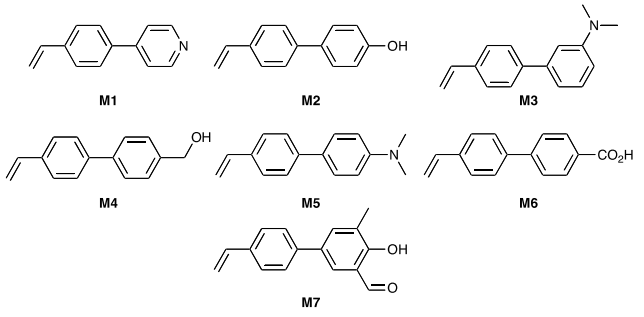

Figure 1. Structures of the biaryl compounds: 4-(4'-ethenylphenyl)-pyridine (**M1**), 4'-ethenyl-(1,1'-biphenyl)-4-ol (**M2**) 4'-ethenyl-N,N-dimethyl-(1,1'-biphenyl)-3-amine (**M3**), 4'-ethenyl-(1,1'-biphenyl)-4-methanol (**M4**), 4'-ethenyl-N,N-dimethyl-(1,1'-biphenyl)-4-amine (**M5**), 4'-ethenyl-(1,1'-biphenyl)-4-carboxylic acid (**M6**), 4'-ethenyl-4-hydroxy-5-methyl-(1,1'-biphenyl)-3-carboxaldehyde (**M7**).

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The pK_a is a crucial parameter that characterises a range of compound properties including solubility, stability and lipophilicity, and in some cases, the fate of a compound in a reaction pathway.[11,12] Of the various analytical techniques available to determine pK_a, (including capillary electrophoresis, liquid-liquid partitioning, and spectrophotometry), potentiometry is most commonly utilised, primarily because of its simplicity and relatively low cost.[11,13] While pK_a determination of water-soluble compounds by potentiometry is relatively straightforward, difficulties are encountered with less polar organic compounds such as the biaryls because of their limited solubility. This problem can be circumvented by the use of binary or even ternary mixtures of organic solvents and water, which increase the solubility of the compound of interest, thereby enabling potentiometric titrations to be undertaken.[14]

Determination of pK_a by semi-aqueous potentiometric titration involves the measurement of apparent dissociation constants (p_sK_as) in various water-organic solvent mixtures. Extrapolation to zero organic solvent is then subsequently undertaken to obtain the aqueous pK_a value; an approach known as the Yasuda -Shedlovsky method.[15]

Herein we report the determination of the acid dissociation constants (pK_as) of the biaryl monomers **M1**-**M7** using mixed solvent potentiometric titration. Potentiometric titrations were conducted in binary mixtures of THF and water to obtain the apparent acid dissociation constant (p_sK_a), then extrapolated to zero organic content to obtain the aqueous pK_a values.

Results and Discussion

Solubility tests

The solubility of 0.0500 and 0.100 mmol biaryl monomers **M1**-**M7** in various organic solvent-water systems (10.00 g) was investigated to identify the appropriate organic co-solvent for potentiometric titration. Of the three organic solvents tested (THF, acetonitrile and methanol), THF was found to be most suitable because of its ability to solvate the biaryl compounds under high aqueous dilution conditions. **M1** exhibited complete dissolution at ≥ 35.0 % THF in water at a concentration of 0.0100 M, while **M2**, **M3** and **M4** showed complete dissolution at ≥ 40.0 % THF at the same concentration. **M5**, **M6** and **M7** exhibited more limiting solubilities at ≥ 40.0 % THF in water at 0.00500 M.

The solubility of the NaOH titrant in the THF-water mixtures was also investigated. A solution of 0.150 M NaOH was prepared in THF-water compositions of ≥ 35.0% THF, based on the results of the solubility tests for the biaryl monomers. The 0.15 M NaOH solution was found soluble up to compositions of 55.0 % THF in water.

Thus, THF-water mixtures of 35.0 - 55.0 % THF were chosen as the binary solvent systems for the potentiometric titration of 0.0100 M **M1**, while a 40.0 - 55.0 % THF composition was selected for 0.0100 M **M2**, **M3** and **M4**, and 0.0050 M **M5**, **M6** and **M7**. The NaOH titrant (0.150 M) was prepared in the same THF-water composition as the analyte solution.

Dielectric and autoprotolysis constants of THF-H_2O mixtures

The calculation of the apparent acid dissociation constant (p_sK_a) of each monomer at various THF-water ratios (eqn 1) requires the dielectric (έ) and autoprotolysis (pK_w) constants of water at the specified organic solvent-water ratios as input parameters.[16] These values were obtained from literature sources.[17,18] Table 1 summarises the έ and pK_w at 25°C for THF-water mixtures in the range 35-55% THF. As expected, the έ and pK_w of water show a decreasing trend with increasing THF concentration, resulting from reduced solution polarity, which suppresses the ionisation capacity of dissolved compounds.

Method Validation: Determination of pK_as of Model Analytes

Semi-aqueous potentiometric titrations using binary mixtures with έ > 50, i.e. water-rich mixtures, have been reported to give relatively accurate pK_a results.[19] In cases where water content is lower (έ < 50), the Yasuda-Shedlovsky extrapolation methodology is usually validated by an analogue because of potential errors associated with long-range extrapolation.[14] For example, in the case of diphacinone and chlorophacinone, ibuprofen was used to validate the potentiometric titration methodology for pK_a determination in a dioxane-water solvent system.[16] Once validated, (i.e. a good correlation of experimental pK_a (4.47) and literature pK_as (4.31-4.91) for ibuprofen was obtained), the method was successfully applied to determine the pK_as of diphacinone and chlorophacinone.

Table 1. Dielectric constant, έ, and autoprotolysis constant, pK_w, of water at 25 °C in THF-water systems.[17,18]

THF, % (v/v)	έ	pK_w
35	53.7	14.6
40	50.5	14.7
45	46.3	14.9
50	42.3	15.0
55	38.9	15.2

As Table 1 shows, the highest έ obtained was 53.7 for the 35% THF solution, with solutions containing higher concentrations of THF recording έ values below 50 because of the limited monomer solubility in water. To establish the validity of the potentiometric titration method under the solution conditions shown in Table 1, biaryl compounds containing acidic and basic functional groups, 2-aminobiphenyl (**A8**) and 4-biphenylcarboxylic acid (**A9**), respectively, with known literature aqueous pK_a values were selected for testing (Figure 2).

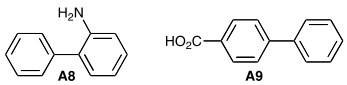


Figure 2. Biaryl model compounds 2-aminobiphenyl (**A8**) and 4-biphenyl carboxylic acid (**A9**).

0.0100 M solutions of **A8** and **A9** were prepared in THF-water mixtures comprised of 40.0, 45.0, 50.0 and 55.0 % THF, respectively. Prior to titration with the standard 0.15 M NaOH,

each analyte solution was pre-acidified to pH 2.5. Thus, whilst **A9** remains in its acidic form, basic **A8** undergoes protonation to its conjugate acid **A8H**.

The titration data (ESI†, Fig ESI3) was fitted using the global minimisation algorithm (Globplot).[20] The Matlab-based program simultaneously fits the complexed and free ligand species concentrations in solution at equilibrium. The fitting routine accounts for the equivalence point of the reaction of excess H^+ (due to acidification with HCl) and the titrant and is therefore, able to resolve the equivalence point of the reaction between the analyte and the titrant to predict the analyte p_sK_a.

Figure 3 shows the Yasuda-Shedlovsky plots for the potentiometric titration of **A8H** and **A9** across the varying solution composition (expressed as a function of dielectric constant). **A8H**, the conjugate acid of a weak base, and **A9**, a weak acid, are characterised by negative and positive slopes, respectively, a feature observed in previously studied semi-aqueous solvent systems.[12] The negative slope of the Yasuda-Shedlovsky plot for **A8H** indicates an increase in its acidity, concomitant to a reduced basicity of **A8**, as a function of increasing THF content, while the positive slope for **A9** indicates a reduced acidity. This result is expected, since an increase in THF content decreases the ε value of the binary mixture (Table 1), leading to enhanced ionisation for **A8H** to form the neutral basic **A8**, and suppression of ionisation for the neutral acidic **A9**.

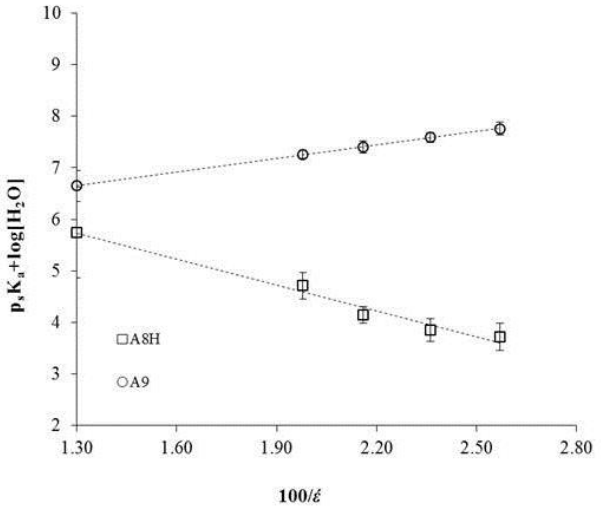


Figure 3. Yasuda-Shedlovsky plots for **A8H** (R^2 = 0.91, slope = -1.64 ± 0.44) and **A9** (R^2 = 0.99, slope = 0.86 ± 0.17). Values for x = 100/ε in 40, 45, 50 and 55 wt % THF in water. The x-intercepts at 100/ε = 1.30 are the p_sK_a + log [H_2O] values at zero THF content (aqueous) and are 5.74 ± 0.88 and 6.65 ± 0.30 for **A8H** and **A9**, respectively (ESI†, Table ESI1).

The extrapolated aqueous pK_as of **A8H** and **A9** are 3.98 and 4.90, respectively, were found to be in close agreement with the literature pK_a values of 3.83 for **A8H**,[21] and 4.19 for **A9**.[22] ΔpK_a values (between experimental and literature) of 0.15 and 0.71 for **A8H** and **A9**, respectively, also compared favourably with validation results reported in the case of ibuprofen (ΔpK_a of 0.55-0.85) in a dioxane-water solvent system.[16]

Determination of pK_as of Biaryl Compounds M1-M7

Due to solubility limitations, potentiometric titrations of the biaryl compounds were carried out at 35.0 - 55.0 % THF for 0.0100 M **M1**, and 40.0 - 55.0 % THF for 0.0100 M **M2**, **M3** and **M4** and 0.0050 m **M5**, **M6** and **M7**. Figure 4 shows the highly linear (R^2 > 0.90) Yasuda-Shedlovsky plots (examples of titration data are given as ESI†, Figs ESI4 and ESI5) for **M1**-**M7** across the varying solution composition (expressed as a function of dielectric constant). The extrapolated aqueous pK_a and the slope of the corresponding Yasuda-Shedlovsky plot for each of the biaryl compounds are listed in Table 2.

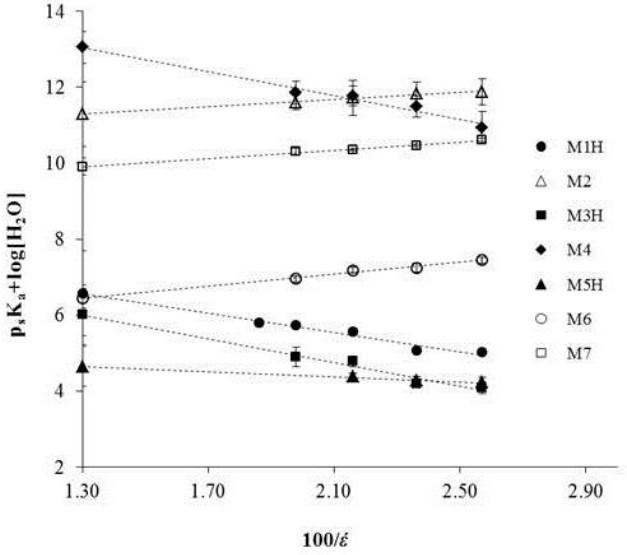


Figure 4. Yasuda-Shedlovsky plots for the biaryl compounds in their acidic forms: **M1H** (R^2 = 0.92), **M2** (R^2 = 0.94), **M3H** (R^2 = 0.93), **M4** (R^2 = 0.91), **M5H** (R^2 = 0.91), **M6** (R^2 = 0.96) and **M7** (R^2 = 0.95). Values for x = 100/ε in 35, 40, 45, 50 and 55 wt % THF in water. The x-intercepts at 100/ε = 1.30 are the p_sK_a + log [H_2O] values at zero THF content (aqueous) (ESI†, Tables ESI2 and ESI3).

Table 2. Slopes of the Yasuda-Shedlovsky plots and aqueous pK_as of the biaryl compounds.

Compound	Slope	pK_a
M1H	-1.25 ± 0.08	4.82 ± 0.82
M2	0.49 ± 0.46	9.53 ± 0.71
M3H	-1.53 ± 0.35	4.26 ± 0.56
M4	-1.53 ± 0.60	11.30 ± 0.73
M5H	-0.35 ± 0.26	2.93 ± 0.34
M6	0.79 ± 0.13	4.69 ± 0.18
M7	0.52 ± 0.10	8.17 ± 0.18

In general, the Yasuda-Shedlovsky plots of the conjugate acids of the basic (i.e. nitrogen-containing) biaryl compounds (Figure 4, Table 2) are characterised by negative slopes, indicating increased acidity of the conjugate acids and reduced basicity of **M1**, **M3** and **M5** with increasing organic content. An increase in THF content decreases the ε value of the binary

mixture leading to preferential formation of the neutral compounds by deprotonation of the conjugate acids. Consequently, the pK_as of the conjugate acids of these basic analytes are higher than the p$_s K_a$ values derived in the THF-water mixtures investigated.

The slopes of the Yasuda-Shedlovsky plots for compounds of comparable size, possessing the same functional groups are expected to be broadly similar.[23] However, the slopes of the plots of the conjugate acids of the dimethylamine isomers **M3H** and **M5H** were observed to differ, a feature attributable to a number of potential effects. The slope of the Yasuda-Shedlovsky plot is reported to be inversely proportional to the average ionic diameter of the solvated molecule.[12,23] The relative polarity of attached substituents and the effect this has on interactions with solvent molecules during solvation is also of significance.[12] Modelling of the solvent accessible surface areas of the two systems (data not shown) revealed that the *para* positioning of the dimethylamine unit in **M5** increases the average diameter of the molecule by approximately 18% relative to the *meta* substituted **M3** isomer, indicating a broad correlation. The most notable difference in the behaviour between **M3** and **M5** can, however, be attributed to the relative substitution pattern of the dimethylamine unit (*meta* and *para*, respectively) and its effect on the ability of the nitrogen lone pair of the amine to conjugate with the pi electrons of the biphenyl ring system. Positioning of the amine group in the *para* position (**M5**) affords significant delocalisation of the nitrogen lone pair electrons through both arene rings, making the electron pair less available to participate in proton capture and hence less basic (ESI†, Fig ESI6). By contrast, positioning of the amine unit meta to the phenyl ring in **M3** limits the movement of the lone pair to the first arene ring (ESI†, Fig ESI7). The lower level of incorporation results in the electron pair being more available for proton capture, resulting in **M3** exhibiting a stronger basic character than **M5**.

The same logic can be applied to explain the higher basicity of **M1**. The pyridine unit, while of aromatic character, cannot incorporate the lone pair of electrons on the ring nitrogen, leaving them fully available and accessible for sharing. Further, the electron lone pair of **M1** remains sterically unhindered relative to the lone pair electrons of the dimethylamine units of **M3** and **M5**.

Figure 4 also shows the Yasuda-Shedlovsky plots of acidic biaryl analytes **M2**, **M6** and **M7**, which are characterised by positive slopes. A positive slope is indicative of decreasing acidity with increasing organic solvent concentration in the mixture. Because the value of the dielectric constant of THF-water mixtures is lower compared to pure water, the extent of ionisation of the analytes is, correspondingly, also lowered in order to remain in their uncharged molecular forms, resulting in lower acidity in the binary mixtures. The same trend has been observed in the titration of common acids (e.g. citric acid, phthalic acid, boric acid and acetic acid) in THF-water mixtures.[24,25]

Acidic character was observed to decrease from **M6** > **M7** > **M2**. While all three analytes exhibit resonance stabilisation of the resultant anion upon ionisation, the character of the attached functional group influences the trend in their acidic behaviour. As expected, the presence of the carboxyl unit on **M6** has a profound effect on the acidic character of the monomer, resulting in a pK_a value three orders of magnitude lower than the phenol monomer **M7** (Table 2). **M2** (pK_a = 9.53) show a modest decrease in acidity relative to phenol (pKa = 9.98).[26] The drop in acidity has been attributed to the presence of the styrene unit, which promotes deprotonation through more effective charge delocalisation in the corresponding phenolate anion (ESI†, Fig ESI8). The higher acidity of **M7** relative to **M2** is due to the influence of the ortho carbonyl unit, which, through a combination of hydrogen bonding (between the carbonyl oxygen and phenolic H, 2.015Å apart) and inductive effects, removes electron density from the phenol OH bond (ESI†, Fig ESI9).

M4, an alcohol, is expected to be a very weak acid and acts as an amphoteric compound as indicated by its negative slope, characteristic of a basic compound. It is a weaker acid (pK_a = 11.28) than **M2** (pK_a = 9.53) as it bears an alkyl alcohol group and not a phenol. The $-CH_2-$ group acts as an insulator to possible resonance stabilisation of lone pair electrons from oxygen and even donates electron density to the oxygen atom, thereby suppressing hydroxyl group ionisation. Upon acidification prior to titration, **M4** behaved as a base by accepting the hydrogen ion from the acid, and as with **M1**, **M3** and **M5**, prefers to be deprotonated in mixtures rich in organic solvent. Thus, its acidity was observed to increase (negative slope, decreasing pK_a) with increasing THF content.

Experimental

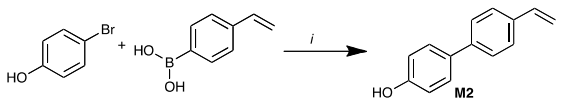
Chemicals and Reagents

All solvents and chemicals were of analytical grade. K_2CO_3, NaOH, HCl, 2-aminobiphenyl and 4-biphenyl carboxylic acid were purchased from Sigma-Aldrich (Australia) and used as received. Acetonitrile, methanol and tetrahydrofuran (THF) were obtained from Sigma Aldrich (Australia) and were used as received. Carbon dioxide-free deionised water was used freshly prepared by boiling deionised water to 95°C.

Synthesis of Biaryl Compounds M1-M7

Compounds **M1-M7** were synthesised by microwave-assisted Suzuki cross-coupling reaction according to Figure 9. In a typical reaction,[9] a mixture of 4-vinylphenylboronic acid (1.00 mmol), arylbromide (1.00 mmol), Pd(DIPHOS)$_2$ (1 mol%), 2 m K_2CO_3 (2.4 mmol, 1.2 mL), distilled water (1.8 mL) and THF (3 mL) were placed in a 10-mL microwave test tube containing a magnetic stirrer bar and purged with nitrogen gas prior to reaction. The 10-mL pressure vessel was then placed in the microwave cavity of a CEM Discover Benchmate reactor and sealed with a pressure lock. The microwave source was set to 100°C using 100 W of power to heat the reaction for 30 min. The reaction mixture was allowed to cool, then washed through Celite with ethyl acetate. The filtrate was evaporated to dryness using a rotary evaporator, re-dissolved in water, extracted with ethyl acetate (2 x 10 mL), dried with anhydrous

Na_2SO_4 and evaporated to reduce the solvent volume for column chromatography.



Scheme 1. Reagents and conditions: (i) $Pd(DIPHOS)_2$, K_2CO_3, $THF:H_2O$ (1:1), 100 ºC, 100 W, 30 min

pK_a Measurements

Solubility Tests. The organic co-solvent for the titration was chosen based on the solubility of 0.0500 and 0.100 mmol test compounds in 10.00 g (0.00500 and 0.0100 M, respectively) of binary mixtures of water and organic solvents at various weight ratios. The organic solvents tested were methanol, acetonitrile and THF.

Potentiometric titration. Potentiometric titrations were performed using a Metrohm 665 Dosimat autotitrator and carried out at constant temperature (25.00 ± 0.50 ºC) under a nitrogen atmosphere. A 125 mm (6.0234.100) slim Metrohm micro-pH glass electrode was used for the titrations, interfaced with a National Instruments NI-DAQ 7 board amplifying and translating the electrode signal, which was recorded in mV. The mV signal was used directly in the analysis of the titration data and transformed into pH using our software. In a typical titration, 10.00 mL of a 0.0100 M or 0.00500 M analyte solution was pre-acidified to low pH (~2.5) by addition of standardised HCl (0.015 M) then titrated with 0.15 M standard NaOH to high pH (~11). Titrations were conducted in triplicate in different THF-water-mixtures ranging from 35-55 % (w/w) THF.

Determination of p_sK_a and pK_a. The p_sK_a value in each THF-water mixture was calculated using the Global Minimisation algorithm (Matlab) for fitting potentiometric data, developed by McCann *et. al*.[20] The apparent acid dissociation constant (p_sK_a) + log [H_2O] is plotted against the inverse of the dielectric constant of the binary mixture. The aqueous pK_a value was then ascertained by extrapolation using the Yasuda-Shedlovsky method as the x-intercept of the linear plot of eq 1[27],

$$p_sK_a + \log [H_2O] = a/\acute{\varepsilon} + b \qquad \text{eq 1}$$

where p_sK_a is the apparent ionization constant in organic solvent-water mixture, έ is the dielectric constant of the binary mixture, a is the slope and b is the intercept. Errors associated with (p_sK_a) + log [H_2O] and aqueous pK_a values are equivalent to 2*s*, where *s* = standard deviation giving 95% confidence interval.

Conclusions

The pK_a values of vinyl biaryl monomers **M1**-**M7**, synthesised by microwave-assisted Suzuki cross-coupling of the appropriate aryl bromide and 4-vinylphenyl boronic acid, were determined by potentiometric titrations in THF-water mixtures. Aqueous pK_a values of the monomers were obtained from extrapolation via the Yasuda-Shedlovsky method. The Yasuda-Shedlovsky plots show a decrease in acidity of **M2**, **M6** and **M7** and basicity of **M1**, **M3** and **M5**. These trends are expected due to the decrease in the dielectric constant of water in the presence of THF favouring the formation of neutral molecular species leading to weaker deprotonation of the acidic biaryls and stronger deprotonation of the conjugate acids of the basic biaryls. **M4**, a weak acid by virtue of its functionality, was observed to behave as a base and, as with **M1**, **M3** and **M5**, exhibited reduced basicity with increasing THF content.

To the best of our knowledge, this is the first reported study of pK_a values undertaken for polymerisable class of compounds that are insoluble in water but have potential utility in aqueous environment. Knowledge of acid dissociation constants of monomers that form the basis for target (used as template) selective recognition in MIPs is essential for designing highly efficient molecularly imprinted polymeric materials (MIPs) that can work both in aqueous and non-aqueous applications, providing capability to 'mix and match' monomers to template/target and enhance binding interactions.

Acknowledgments

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Potentiometric Determination of Acid Dissociation Constants of Novel Biaryl Monomers

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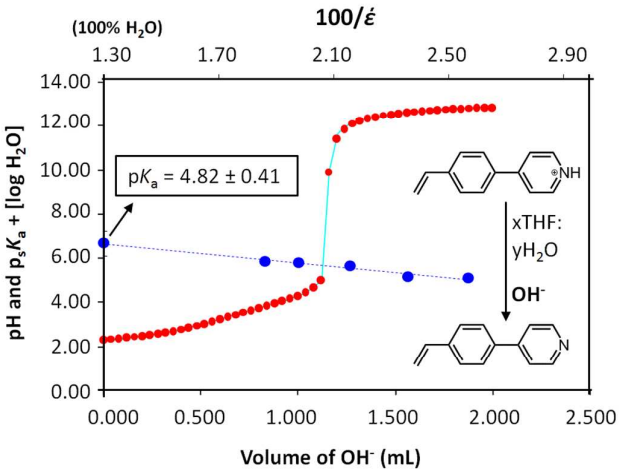
Graphical Abstract



pK$_a$s of novel biaryl monomers for MIPs design for aqueous environment were determined by the Yasuda-Shedlovsky method.