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# A novel indicator series for measuring $pK_a$ values in acetonitrile

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This article is dedicated to Professor Grubbs, for exploring new frontiers in science and inspiring us to follow

**Abstract**—A series of substituted azobenzene dyes was found to span a range of 8  $pK_a$  units in acetonitrile. The UV absorption spectra of the dyes are responsive to protonation, changing in both absorption maximum and intensity. These characteristics make the dyes useful as indicators for the measurement of  $pK_a$  values of neutral organic bases that absorb in the visible region of the spectrum. © 2004 Elsevier Ltd. All rights reserved.

## 1. Introduction

Neutral organic bases play an essential role in a wide range of chemical transformations.<sup>1</sup> The advantages of organic bases over inorganic bases include steric bulk that gives rise to weakly associating ion pairs, enhancing the reactivity of the newly formed anion, increased solubility in organic reaction media, and milder reaction conditions.<sup>2</sup> The effectiveness of a base in a chemical reaction is largely dependant on its  $pK_a$  value, making accurate measurement of  $pK_a$  crucial to the successful design of new reaction methods. While the determination of  $pK_a$  values in water is straightforward, with extensive quantities of data referenced in the literature,<sup>3</sup> many reaction methods employing neutral organic bases are incompatible with aqueous media, creating a demand for improved methods of  $pK_a$  determination in aprotic solvents. Here we describe a series of azobenzene indicator dyes that facilitate the accurate measurement of  $pK_a$  values in acetonitrile.

The design of supramolecular architectures incorporating neutral organic bases represents one focus of research in our laboratory. These macromolecules have potential to act as enzyme mimics capable of binding substrate molecules and promoting chemical transformations. Toward this goal, we synthesized phenylene ethynylene (PE) oligomers **1**, having a substituted pyridine monomer in the backbone of the oligomer. In acetonitrile, the oligomers adopt a helical conformation with the pyridine nitrogen located on the surface of the interior binding cavity.<sup>4</sup> Before attempting to use these molecules to promote chemical transformations, we first wanted to determine the  $pK_a$  value of each oligomer in its folded state in acetonitrile.



 $Tg = -(CH_2CH_2O)_3CH_3$ 

Measurement of  $pK_a$  values in acetonitrile is well documented, with values reported for over 300 compounds.<sup>5</sup> However, the reliability of much of this data is uncertain, as values reported by different authors often deviate by more that one  $pK_a$  unit.<sup>6</sup> These deviations may arise from difficulties in measuring the acidity in acetonitrile media, accounting for the unreliability of  $pK_a$  values determined via direct titration methods. Also, the high concentrations required for some methods can lead to errors resulting from unwanted intermolecular interactions such as homoconjugation between a compound and its ionized species.

Koppel and coworkers have described a method for measuring  $pK_a$  values that minimizes these sources of error, and have used this method to measure  $pK_a$  values for a wide assortment of compounds in aprotic solvents including acetonitrile.<sup>6</sup> In this method, UV–vis spectroscopy is used to measure  $\Delta pK_a$  values for sets of compounds having similar acidities. To obtain a  $\Delta pK_a$  value for two Brønsted

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bases, substoichiometric portions of strong acid are added to a solution of the two bases, and the resulting changes in the UV spectrum are monitored over the course of the titration.<sup>7</sup> Thus, the neutral and protonated species of each of the bases must have different molar absorbtivities  $(\varepsilon)$  over a given range of wavelengths ( $\lambda$ ). After measurements have been made for multiple sets of compounds, an acidity scale is constructed based upon the relative  $pK_a$  differences. To assign absolute  $pK_a$  values to the acidity scale, a compound for which the  $pK_a$  value has been determined reliably is chosen to serve as a reference. By obtaining only the  $pK_a$ value of the reference compound using direct titration methods, errors resulting from inaccuracies in measuring the acidity of acetonitrile media are greatly reduced. Also, the use of UV spectroscopy allows  $\Delta p K_a$  measurements to be carried out at low concentrations, decreasing the possibility of errors arising from unwanted intermolecular interactions. Given that pyridine chromophores are known to undergo a bathochromic shift in UV absorbance upon protonation,<sup>8</sup> the methods developed by Koppel and coworkers appeared to be suitable for measuring the  $pK_a$ values of oligomers 1.

## 2. Results and discussion

In the UV spectra of oligomers 1, the region below 350 nm is dominated by the PE chromophore, so upon protonation of the pyridine moiety, the most easily detectable change occurs at 350–425 nm (Fig. 1). As a result, acquiring  $\Delta p K_a$ measurements between oligomers 1 and other compounds requires that those compounds likewise have an absorbance band in the region of 350-425 nm that is responsive to changes in protonation state. Unfortunately, only a limited number of compounds having reliably determined  $pK_a$ values in acetonitrile meet these criteria,<sup>5</sup> mandating the design of a new series of indicator compounds that absorb in or near the visible region of the spectrum, undergo a shift in absorbance maximum ( $\lambda_{max}$ ) upon protonation, and span the  $pK_a$  range that oligomers 1 are expected to occupy ( $pK_a=5-$ 14, based on reported values for substituted pyridine molecules).7,9

 $\begin{pmatrix} 2 \\ 1.5 \\ 0 \\ 250 \\ 300 \\ 350 \\ 400 \\ 450 \\ \lambda \text{ (nm)} \end{pmatrix}$ 

2.5

Figure 1. UV spectra of 1 (blue) and 1H  $^+ClO_4^-$  (red) in acetonitrile (R=H). [oligomer]  ${\sim}3.0~\mu M.$ 

Substituted azobenzenes possess the needed characteristics to serve as indicator compounds for the oligomer acidity scale. First, their widespread use as dyes is evidence that they absorb strongly in the visible wavelength range. Also, some azobenzene molecules bearing *N*,*N*-dimethyl substituents are known to change color upon protonation, indicating a shift in  $\lambda_{max}$ .<sup>10</sup> Furthermore, the basicity of azobenzene molecules can be modulated by addition of electron donating or electron withdrawing substituents to the benzene rings.<sup>11</sup> In view of these characteristics, azobenzene was chosen as the framework for the needed indicators, and the synthesis of a series of compounds spanning the p $K_a$  range of 5–14 was initiated.

Synthesis of the azobenzene indicators is shown in Table 1. Reaction of aniline **2** with sodium nitrite under acidic conditions provided the corresponding diazonium salt in situ. Then, nucleophilic attack from *N*,*N*-dimethylaniline  $3^{12}$  yielded substituted azobenzenes **4-10**. The large number of commercially available anilines and easily accessible *N*,*N*-dimethylanilines translates into a vast number of potential azobenzene products. However, in the absence of a nitro substituent at the R<sub>1</sub> position, *cis*-*trans* isomerization about the nitrogen-nitrogen double bond is sufficiently slow as to interfere with *pK*<sub>a</sub> measurements. As a result, the nitro substituent was preserved in all of the azobenzene indicators synthesized.





<sup>a</sup> Vaidyanathan, S. Indian J. Chem. **1973**, 11, 400.

<sup>b</sup> Nishimura, N.; Kosako, S.; Sueishi, Y. Bull. Chem. Soc. Jpn. 1984, 57, 1617–1625.

<sup>c</sup> Skulski, K. Bull. Acad. Pol. Sci. Ser. Sci. Chim. 1973, 21, 859-868.

To assess the suitability of azobenzenes **4-10** for use as indicators, UV spectra were acquired for each of the dyes and their conjugate acids. The data in Table 2 reveal that all of the dyes absorb in the visible region of the spectrum and undergo a shift in  $\lambda_{max}$  and intensity ( $\varepsilon$ ) upon protonation, fulfilling two of the requirements necessary for the indicator series.

Using the previously described methods,<sup>7</sup>  $\Delta p K_a$  values were measured for pairs of indicators having similar acidities ( $\Delta p K_a < 2$ ). These measurements were compiled to form an acidity scale, and absolute  $p K_a$  values assigned to each indicator relative to the reference compound of 2,4dinitrophenol ( $p K_a = 16.66$ ).<sup>6</sup> The  $p K_a$  values of indicators

 Table 2. UV absorbance of azobenzene indicators and their conjugate acids in acetonitrile

Indicator	$\lambda_{\max}$ (nm)	$(M^{-1}cm^{-1})$	Conjugate acid	$\lambda_{\max}$ (nm)	$(M^{-1}cm^{-1})$
4	526	36,700	$4 \cdot H^+$	488	43,400
5	499	30,600	5·H <sup>+</sup>	495	50,300
6	475	29,800	6·H <sup>+</sup>	506	63,300
7	489	30,900	$7 \cdot H^+$	503	64,400
8	497	31,300	8·H <sup>+</sup>	475	64,600
9	504	28,600	9·H <sup>+</sup>	498	61,700
10	455	25,800	$10 \cdot H^+$	461	59,100

**4-10** vary from 8.2 to 16.2 (Table 3), spanning the majority of the expected  $pK_a$  range of oligomers **1** and fulfilling the final requirement set forth in the design of the indicator series.

**Table 3.**  $pK_a$  values of azobenzene indicators<sup>13</sup>

Indicator	$pK_a$ (CH <sub>3</sub> CN)
4	8.2
5	9.1
6	10.3
7	11.3
8	13.1
9	14.1
10	16.2

In Figure 2, the  $pK_a$  values of the indicators are plotted against the sum of the  $\sigma$  or  $\sigma^+$  values for the substituents located on both benzene rings.<sup>14</sup> We were initially surprised to find such poor correlation in the Hammett plots. However, the primary resonance contributor of the protonated indicators<sup>15</sup> reveals that the substituents on the *N*,*N*dimethylaniline ring are in resonance with the positive charge, whereas the substituents on the opposite phenyl ring



**Figure 2.** Correlation between indicator  $pK_a$  and  $\sigma$  (a) or  $\sigma^+$  (b).



Figure 3. Primary resonance contributor of protonated *N*,*N*-dimethylazobenzene indicator.

interact with the positive charge solely through induction (Fig. 3). This differentiation between the phenyl rings of the azobenzene indicator provides a likely rationale for the observed inconsistencies.

#### 3. Conclusions

In conclusion, substituted azobenzene dyes were used to generate a novel indicator series. The indicators span a broad range of  $pK_a$  values in acetonitrile, and are useful for measuring the basicity of compounds that absorb in the visible region of the spectrum. The basicity data acquired using these indicators may aid in the design of new reaction methods involving neutral organic bases. Future work may include expansion of the indicator series to encompass an increased  $pK_a$  range and use of the indicators in a wider variety of aprotic solvents.

#### 4. Experimental

## 4.1. General

Unless otherwise noted, all starting materials were obtained from commercial suppliers and were used without further purification. Flash column chromatography was carried out with silica gel 60 (230–400 mesh) from EM Science.

The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Unity 400, Varian Unity 500, or Varian Narrow Bore 500 spectrometer. Chemical shifts are expressed in parts per million ( $\delta$ ) using residual solvent protons as internal standard ( $\delta$  7.26 ppm for CHCl<sub>3</sub>). Coupling constants, J, are reported in Hertz (Hz), and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), and app (apparent). Mass spectra were obtained through the Mass Spectrometry Facility, School of Chemical Sciences, University of Illinois. Low resolution fast atom bombardment (FAB) and low and high resolution electron impact (EI) mass spectra were obtained on a Micromass 70-VSE spectrometer. High resolution fast atom bombardment (FAB) mass spectra were obtained on a Micromass 70-SE-4F spectrometer. Low resolution matrix assisted laser desorption (MALDI) mass spectra were obtained using a Applied Biosystems Voyager-DE STR spectrometer. Elemental analyses were performed by the University of Illinois Micro Analytical Service Laboratory.

# 4.2. $pK_a$ measurements using UV-vis spectroscopy

UV absorption spectra were recorded on a Shimadzu (model UV-160A) spectrophotometer using 1-cm quartz cells. For the titration experiments, stock solutions of each of the indicators were prepared using spectrophotometric grade acetonitrile purchased from Fisher Scientific. A UV spectrum of each compound was obtained at a dilution such that the maximum absorbance was <1. Concentrated HClO<sub>4</sub> was then added, and a UV spectrum of the protonated base acquired. To measure  $\Delta pK_a$  values, a 1:1 mixture of two indicators was prepared ( $c=8-20 \ \mu$ M) in spectrophotometric grade acetonitrile, and small portions of HClO<sub>4</sub> added until no further change was observed in the UV spectrum. The initial concentrations of each indicator were verified using Eq. 1 for the UV spectrum prior to addition of any acid.

$$A^{\lambda} = \varepsilon^{\lambda}_{B_1}[B_1] + \varepsilon^{\lambda}_{B_2}[B_2] \tag{1}$$

 $\Delta p K_a$  values were then calculated for each of the spectra over the course of the titration using methods outlined by Koppel and coworkers.<sup>7</sup> The final value of  $\Delta p K_a$  represents the average of values obtained from spectra where each of the species present meets a threshold concentration. This concentration was typically 10% of the initial concentration, but for  $\Delta p K_a > 1.7$ , a lower threshold concentration was invoked. Absolute  $p K_a$  values were assigned to each compound relative to the 2,4-dinitrophenol reference compound.



**4.2.1. Dimethyl-[4-(2-cyano-4-nitro-phenylazo)-phenyl]amine (4).** A 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter

2-cyano-4-nitroaniline (0.457 g, charged with was 2.66 mmol), concd HCl (0.5 mL), and DMF (8 mL), then chilled to 5 °C in an ice bath. A solution of NaNO<sub>2</sub> (0.185 g, 2.68 mmol) in 3:1 DMF:H<sub>2</sub>O (2 mL) was added, and the reaction mixture stirred at 0-5 °C for 30 min. A second 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with N,N-dimethylaniline (0.337 mL, 2.66 mmol), 1 M aq. HCl (8 mL), and DMF (8 mL), then chilled to 5 °C in an ice bath. The solution of 2-cyano-4-nitroaniline diazonium salt was transferred to the second flask over 5 min, and the reaction mixture basified with 4 M aq. K<sub>2</sub>CO<sub>3</sub>. The solution was warmed to 15 °C, diluted with 100 mL H<sub>2</sub>O, and extracted with 3×100 mL CHCl<sub>3</sub>. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give a purple solid. Recrystallization from EtOAc gave 0.144 g of dark purple solid (18%).<sup>16</sup> Mp 194-196°C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) d 8.62 (dd, J=2.5, 0.4 Hz, 1H), 8.43 (dd, J=9.1, 2.5 Hz, 1H), 8.05-7.99 (m, 3H), 6.80 (AA'XX',  $J_{AA'}=2.6$  Hz,  $J_{AX}=9.6$  Hz,  $J_{AX'}=0.2$  Hz,  $J_{XX'}=2.6$  Hz, 2H), 3.20 (s, 6H). HRMS (EI) m/z 295.1099 (Calcd [M]<sup>+</sup>=295.1069).

4.2.2. Dimethyl-[4-(2-chloro-4-nitro-phenylazo)phenyl]-amine (5). A 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with 2-chloro-4-nitroaniline (0.350 g, 2.03 mmol), 1 M aq. HCl (8 mL), and CH<sub>3</sub>CN (4 mL), then chilled to 5  $^{\circ}\mathrm{C}$  in an ice bath. A solution of NaNO<sub>2</sub> (0.143 g, 2.07 mmol) in H<sub>2</sub>O (1.5 mL) was added dropwise over 2 min, and the reaction mixture stirred at 0-5 °C for 30 min. A second 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with N,N-dimethylaniline (0.257 g, 2.03 mmol), 1 M aq. HCl (8 mL), and CH<sub>3</sub>CN (8 mL), then chilled to 5 °C in an ice bath. The solution of 2-chloro-4-nitroaniline diazonium salt was transferred to the second flask over 5 min, then chilled 4 M aq. K<sub>2</sub>CO<sub>3</sub> added to bring to pH 4. The solution was removed from the ice bath and stirred for 1 h. After addition of 100 mL  $H_2O$ , the solution was extracted with 3×100 mL CHCl<sub>3</sub>. The combined organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated to give a dark purple solid. Purification by silica gel chromatography (3:1 hexanes:EtOAc) gave 0.507 g of dark purple solid (82%).<sup>17</sup> Mp 191-192 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) d 8.40 (dd, J=2.5, 0.3 Hz, 1H), 8.16 (dd, (400 MHz, CDCl<sub>3</sub>) d 8.40 (dd, J=2.3, 0.5 Hz, 1H), 6.16 (dd, J=9.0, 2.4 Hz, 1H), 7.97 (AA'XX',  $J_{AA'}=2.6$  Hz,  $J_{AX}=9.4$  Hz,  $J_{AX'}=0.1$  Hz,  $J_{XX'}=2.6$  Hz, 2H), 7.79 (d, J=8.9 Hz, 1H), 6.82 (AA'XX',  $J_{AA'}=2.6$  Hz, 2H), 7.79 (d,  $J_{AX}=0.3$  Hz,  $J_{XX'}=2.6$  Hz, 2H), 3.16 (s, 6H). <sup>13</sup>C NMR (125.7 MHz, CDCl<sub>3</sub>) δ 153.9, 153.3, 147.2, 144.4, 134.0, 126.9, 126.1, 122.7, 118.1, 111.6, 40.4. HRMS (EI) m/z 304.0731 (Calcd [M]<sup>+</sup>=304.0727).

**4.2.3.** Dimethyl-[4-(4-nitro-phenylazo)-phenyl]-amine (6). A 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with 4-nitroaniline (0.258 g, 1.87 mmol), 1 M aq. HCl (8 mL), and CH<sub>3</sub>CN (4 mL), then chilled to 5 °C in an ice bath. A solution of NaNO<sub>2</sub> (0.135 g, 1.96 mmol) in H<sub>2</sub>O (1.5 mL) was added dropwise over 2 min, and the reaction mixture stirred at 0-5 °C for 30 min. A second 50 mL threenecked round bottom flask equipped with two glass stoppers

and a thermometer adapter was charged with N.Ndimethylaniline (0.240 g, 1.89 mmol), 1 M aq. HCl (8 mL), and CH<sub>3</sub>CN (8 mL), then chilled to 5 °C in an ice bath. The solution of 4-nitroaniline diazonium salt was transferred to the second flask over 5 min, then chilled 4 M aq. K<sub>2</sub>CO<sub>3</sub> added to bring to pH 2. The solution was removed from the ice bath and stirred for 2 h. After addition of 100 mL H<sub>2</sub>O, the solution was basified with 4 M aq. K<sub>2</sub>CO<sub>3</sub> and extracted with 3×100 mL CHCl<sub>3</sub>. The combined organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated to give a dark purple solid. The crude product was filtered through a plug of silica gel with 3:1 hexanes:EtOAc, then recrystallized from EtOAc to give 0.289 g of dark purple solid (57%).<sup>18</sup> Mp 229-230 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.32 (AA'XX',  $J_{AA'}=2.4$  Hz,  $J_{AX}$ =9.1 Hz,  $J_{AX'}$ =0 Hz,  $J_{XX'}$ =2.4 Hz, 2H), 8.00-7.92 (m, 4H), 6.78 (d, J=9.3 Hz, 2H), 3.14 (s, 6H). <sup>13</sup>C NMR (125.7 MHz, CDCl<sub>3</sub>) d 157.0, 153.5, 147.5, 143.9, 126.2, 124.9, 122.8, 111.6, 40.4. HRMS (EI) m/z 270.1115 (Calcd  $[M]^+=270.1117).$ 

4.2.4. Dimethyl-[3-methyl-4-(4-nitro-phenylazo)phenyl]-amine (7). A 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with 4-nitroaniline (0.602 g, 4.36 mmol), 1 M aq. HCl (10 mL), and CH<sub>3</sub>CN (5 mL), then chilled to 5 °C in an ice bath. A solution of NaNO<sub>2</sub> (0.304 g, 4.40 mmol) in H<sub>2</sub>O (1.5 mL) was added dropwise over 2 min, and the reaction mixture stirred at 0-5 °C for 30 min. A second 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with N,N-dimethyl-m-toluidine (0.590 g, 4.36 mmol), 1 M aq. HCl (10 mL), and CH<sub>3</sub>CN (10 mL), then chilled to 5 °C in an ice bath. The solution of 4-nitroaniline diazonium salt was transferred to the second flask over 5 min, at which point a pink precipitate formed. The solution was basified with 4 M aq. K<sub>2</sub>CO<sub>3</sub>, diluted with 100 mL H<sub>2</sub>O, and extracted with  $3 \times 100$  mL CHCl<sub>3</sub>. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give a purple solid. Recrystallization from MeOH:EtOAc (15:1, 800 mL) gave 0.984 g of purple solid (79%).<sup>4</sup> Mp 173-174 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.30 (AA'XX',  $J_{AA'}$ =2.3 Hz,  $J_{AX}$ =9.1 Hz,  $J_{AX'}$ =0.1 Hz,  $J_{XX'}$ =2.3 Hz, 2H), 7.90 (AA'XX',  $J_{AA'}$ =2.3 Hz, 2H), 7.90 (AA'XX',  $J_{AA'}$ =2.3 Hz,  $J_{AX}$ =9.1 Hz,  $J_{AX'}$ =0 Hz,  $J_{XX'}$ =0.3 Hz, 2H), 7.82 (d, J=8.7 Hz, 1H), 6.60-6.55 (m, 2H), 3.11 (s, 6H), 2.71 (s, 3H). <sup>13</sup>C NMR (125.7 MHz, CDCl<sub>3</sub>) δ 157.3, 153.6, 147.2, 143.2, 142.2, 124.8, 122.7, 117.5, 112.6, 110.2, 40.3, 18.4. HRMS (EI) *m*/*z* 284.1286 (Calcd [M]<sup>+</sup>=284.1273).

**4.2.5.** Dimethyl-[3-methoxy-4-(4-nitro-phenylazo)phenyl]-amine (8). A 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with 4-nitroaniline (0.279 g, 2.02 mmol), 1 M aq. HCl (8 mL), and CH<sub>3</sub>CN (4 mL), then chilled to 5 °C in an ice bath. A solution of NaNO<sub>2</sub> (0.140 g, 2.03 mmol) in H<sub>2</sub>O (1.0 mL) was added dropwise over 2 min, and the reaction mixture stirred at 0-5 °C for 30 min. A second 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with *N*,*N*-dimethyl-*m*-anisidine (0.305 g, 2.02 mmol), 1 M aq. HCl (8 mL), and CH<sub>3</sub>CN (8 mL), then chilled to 5 °C in an ice bath. The solution of

4-nitroaniline diazonium salt was transferred to the second flask over 5 min, then chilled 4 M aq. K<sub>2</sub>CO<sub>3</sub> added to bring to pH 3. The solution was removed from the ice bath and stirred for 30 min. After addition of 100 mL H<sub>2</sub>O, the solution was basified with 4 M aq. K<sub>2</sub>CO<sub>3</sub> and extracted with 3×100 mL CHCl<sub>3</sub>. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give a purple solid. Recrystallization from EtOAc gave 0.410 g of dark purple crystals (68%). Mp 169-170 °C. <sup>1</sup>H NMR (400 MHz,  $\dot{CDCl_3}$ )  $\delta$  8.28 (AA'XX',  $J_{AA'}=2.4$  Hz,  $J_{AX}=9.1$  Hz,  $J_{AX'}=0.1$  Hz,  $J_{XX'}=2.4$  Hz, 2H), 7.89 (d, J=9.0 Hz, 2H), 7.84 (d, J=9.1 Hz, 1H), 6.35 (dd, J=9.3, 2.4 Hz, 1H), 6.18 (d, J=2.4 Hz, 1H), 4.04 (s, 3H), 3.14 (s, 6H). <sup>13</sup>C NMR (125.7 MHz, DMSO-*d*<sub>6</sub>) δ 160.5, 156.9, 155.6, 146.2, 133.1, 125.0, 122.3, 117.8, 105.3, 94.4, 55.8, 40.0. IR (nujol) 2723, 1601, 1583, 1552, 1509, 1326, 1271, 1189, 1095, 805, 754 cm<sup>-1</sup>. HRMS (EI) m/z 300.1230 (Calcd [M]<sup>+</sup>=300.1222).

4.2.6. Dimethyl-[3-methoxy-4-(2-methoxy-4-nitrophenylazo)-phenyl]-amine (9). A 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with 2-methoxy-4nitroaniline (0.256 g, 1.52 mmol), 1 M aq. HCl (6 mL), and CH<sub>3</sub>CN (3 mL), then chilled to 5 °C in an ice bath. A solution of NaNO<sub>2</sub> (0.110 g, 1.59 mmol) in  $H_2O$  (1.0 mL) was added dropwise over 2 min, and the reaction mixture stirred at 0-5 °C for 30 min. A second 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with N,N-dimethyl-manisidine (0.234 g, 1.55 mmol), 1 M aq. HCl (6 mL), and CH<sub>3</sub>CN (6 mL), then chilled to 5 °C in an ice bath. The solution of 2-methoxy-4-nitroaniline diazonium salt was transferred to the second flask over 5 min, then chilled 4 M aq.  $K_2CO_3$  added to bring to pH 3. The solution was removed from the ice bath and stirred for 1 h. After addition of 100 mL H<sub>2</sub>O, the solution was basified with 4 M aq.  $K_2CO_3$  and extracted with  $3 \times 100$  mL CHCl<sub>3</sub>. The combined organic phase was dried over MgSO4, filtered, and concentrated to give a dark green solid. Recrystallization from EtOAc gave 0.439 g of dark green crystals (87%). Mp 177-178 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.88-7.83 (m, 3H), 7.70–7.67 (m, 1H), 6.34 (dd, J=9.4, 2.6 Hz, 1H), 6.17 (d, J=2.6 Hz, 1H), 4.07 (s, 3H), 4.03 (s, 3H), 3.14 (s, 6H).<sup>13</sup>C NMR (125.7 MHz, DMSO- $d_6$ )  $\delta$  160.3, 155.3, 155.1, 147.1, 146.9, 133.8, 118.0, 117.0, 116.4, 107.9, 105.2, 94.4, 56.4, 55.7, 40.0. IR (nujol) 2723, 1601, 1326, 1273, 1214, 1124, 1082, 860, 803, 744, 730 cm<sup>-1</sup>. HRMS (EI) m/z330.1324 (Calcd [M]<sup>+</sup>=330.1328).

**4.2.7.** Dimethyl-[3,5-dimethoxy-4-(4-nitro-phenylazo)phenyl]-amine (10). A 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with 4-nitroaniline (0.271 g, 1.96 mmol), 1 M aq. HCl (8 mL), and CH<sub>3</sub>CN (4 mL), then chilled to 5 °C in an ice bath. A solution of NaNO<sub>2</sub> (0.136 g, 1.97 mmol) in H<sub>2</sub>O (1.5 mL) was added dropwise over 2 min, and the reaction mixture stirred at 0-5 °C for 30 min. A second 50 mL three-necked round bottom flask equipped with two glass stoppers and a thermometer adapter was charged with *N*,*N*-dimethyl-3,5-dimethoxyaniline (0.355 g, 1.96 mmol), 1 M aq. HCl (8 mL), and CH<sub>3</sub>CN (8 mL), then chilled to 5 °C in an ice bath. The solution of 4-nitroaniline diazonium salt was transferred to the second flask over 5 min, and the reaction mixture basified with 4 M aq. K<sub>2</sub>CO<sub>3</sub>. The solution was warmed to 25 °C, diluted with 100 mL H<sub>2</sub>O, and extracted with 3×100 mL CHCl<sub>3</sub>. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give a purple solid. Purification by silica gel chromatography (EtOAc) gave 0.645 g of dark purple solid (99%). Mp 191–192 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.27 (AA'XX', *J*<sub>AA'</sub>=2.4 Hz, *J*<sub>AX</sub>=9.2 Hz, *J*<sub>AX'</sub>=0.2 Hz, *J*<sub>XX'</sub>=2.4 Hz, 2H), 7.85 (AA'XX', *J*<sub>AA'</sub>=2.4 Hz, *J*<sub>AX</sub>=9.2 Hz, *J*<sub>AX</sub>=9.2 Hz, *J*<sub>AX</sub>=9.2 Hz, *J*<sub>AX</sub>=9.2 Hz, *J*<sub>AX</sub>=9.1 Hz, *J*<sub>AX</sub>=9.2 Hz, *J*<sub>AX</sub>=0.15 (s, 6H). <sup>13</sup>C NMR (125.7 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  158.5, 157.2, 154.6, 145.8, 124.8, 123.9, 121.7, 88.3, 55.9, 40.0. IR (nujol) 2724, 1602, 1581, 1511, 1320, 1252, 1143, 1099, 871 cm<sup>-1</sup>. HRMS (EI) *m/z* 330.1331 (Calcd [M]<sup>+</sup>=330.1328).

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