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Pyridine-Containing *m*-Phenylene Ethynylene Oligomers Having Tunable Basicities

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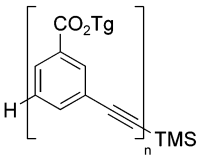
ABSTRACT

Incorporation of a pyridine monomer into the backbone of a *m*-phenylene ethynylene oligomer allows functionalization of the interior binding cavity of the folded oligomer. The basicity of the inwardly directed pyridine moiety was modulated by changing the substituents on the pyridine ring and through oligomer folding, granting access to a pK_a range of 5–14 in acetonitrile.

Nature's alphabet of amino acids contains only five residues having acidic or basic side chains. Yet, using only these five residues, enzymes are able to meet all of their needs for acids and bases to direct substrate binding and reaction catalysis.[1] This remarkable versatility arises in part from the ability of enzymes to modulate the pK_a values of these amino acid side chains.[2] The literature is rich with examples of supramolecular assemblies that selectively bind guest molecules and promote chemical transformations.[3,4] Moreover, Rebek and co-workers have used acid−base interactions to direct substrate binding in cavitand molecular containers.[5] However, we are unaware of any reports of cavitand molecules that incorporate acidic or basic functional groups having tunable pK_a values. Here we describe the synthesis and pK_a determination of a series of *m*-phenylene ethynylene (PE) oligomers that fold into cavitand-like structures and incorporate pyridine moieties with tunable basicities.



1, n≥10

Phenylene ethynylene oligomers **1** previously studied by our group and others[6] have been found to adopt a compact helical conformation in polar solvents such as acetonitrile.[7] From this, we predicted that functionalization of the binding cavity could be accomplished through incorporation of a basic moiety into the PE backbone. Substituted pyridines are

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(2) Joshi, M. D.; Sidhu, G.; Nielsen, J. E.; Brayer, G. D.; Withers, S. G.; McIntosh, L. P. *Biochemistry* **2001**, *40*, 10115−10139.

(3) For reviews, see: (a) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashinda, O. *Chem. Rev.* **1996**, *96*, 721−758. (b) Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 1378−1383. (c) Luning, U. *J Mater. Chem.* **1997**, *7*, 175−182. (d) Motherwell, W. B.; Bingham, M. J.; Six, Y. *Tetrahedron* **2001**, *57*, 4663−4686.

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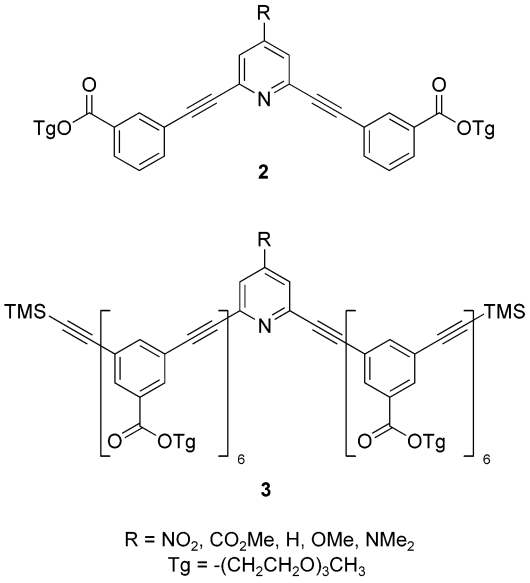
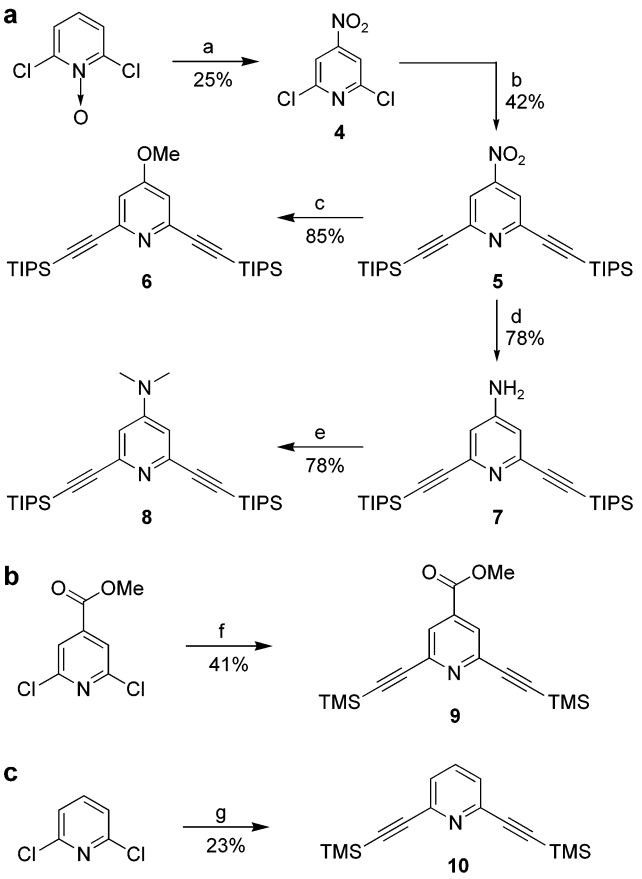
suitable for this purpose as their incorporation into the PE backbone can be achieved without significantly disrupting the folded conformation of the oligomer, and the basicity of the nitrogen lone pair can be modulated by changing the substituents on the pyridine ring.[8] We also wanted to explore the effect of oligomer folding on the basicity of the pyridine moiety, as the helical cavity of a folded oligomer may provide a hydrophobic, solvent-sheltered local environment, and π-stacking interactions could potentially help to stabilize the pyridinium species.[9] To investigate the extent to which pyridine basicity can be modulated through changes in ring electronics and local environment, two sets of oligomers were synthesized having various substituents on the pyridine ring. Of these oligomers, trimers **2** are too short to form a helix, but tridecamers **3** have sufficient length to adopt a helical conformation with the pyridine monomer sandwiched between the two terminal phenyl rings.[10]



Scheme 1. Synthesis of Pyridine Monomers[a]



[a] Reagents and conditions: (a) H_2SO_4, HNO_3, 120 °C. (b) triisopropylsilyl acetylene, $Pd_2(dba)_3$, CuI, PPh_3, Et_3N, 40 °C. (c) K_2CO_3, MeOH, 65 °C. (d) Fe, AcOH, 70 °C. (e) CH_2O, $NaBH_3CN$, AcOH, 35 °C. (f) trimethylsilyl acetylene, $Pd_2(dba)_3$, CuI, PPh_3, Et_3N, 60 °C. (g) trimethylsilyl acetylene, $Pd_2(dba)_3$, CuI, PPh_3, Et_3N, 80 °C.

The first step in generating oligomers **2** and **3** was the synthesis of substituted pyridine monomers **6**, **8**, **9**, and **10** as outlined in Scheme 1. Starting from 2,6-dichloropyridine *N*-oxide,[11] treatment with nitric acid gave 2,6-dichloro-4-nitropyridine (**4**),[12] which was converted to 4-nitropyridine monomer **5** by Pd-catalyzed cross-coupling with triisopropylsilyl acetylene. Reaction of **5** with potassium carbonate in methanol gave 4-methoxypyridine monomer **6**.[13] In a parallel synthesis, reduction of remaining **5** with elemental iron and acetic acid gave **7**,[14] which was subsequently converted to 4-*N*,*N*-(dimethylamino)pyridine monomer **8** via reductive amination[15] (Scheme 1a). Isonicotinic acid methyl ester monomer **9** and unsubstituted pyridine monomer **10** were obtained through Pd-catalyzed cross-coupling of methyl 2,6-dichloroisonicotinate (Scheme 1b) and 2,6-dichloropyridine (Scheme 1c), respectively, with trimethylsilyl acetylene.

To complete the synthesis of oligomers **2** and **3**, the appropriate pyridine monomer was first subjected to TBAF for removal of the silyl protecting groups. Then, Pd-catalyzed cross-coupling with 2 equiv of iodide-terminated PE monomer (**11**) or hexamer (**12**)[7] gave the desired oligomer (Scheme 2). Results for the synthesis of the pyridine-containing oligomers are summarized in Table 1.

To explore the effect of oligomer folding on pyridine basicity, it was necessary to carry out pK_a measurements for oligomers **2** and **3** under solvent conditions that promote helix formation. UV spectroscopy can be used to evaluate the ability of a solvent to promote helix formation in PE

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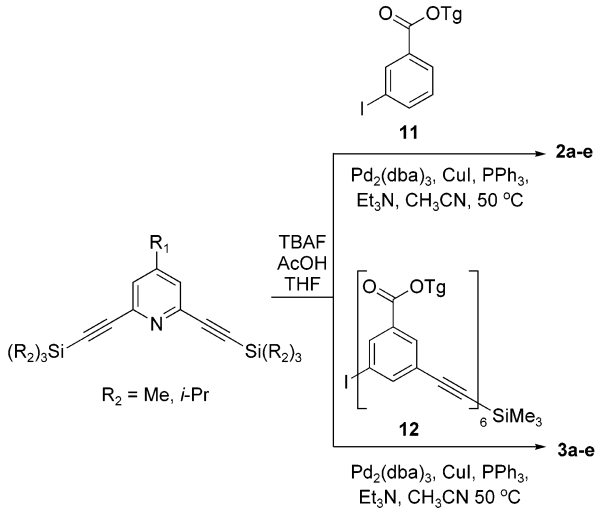
Scheme 2. Synthesis of Pyridine-Containing Oligomers



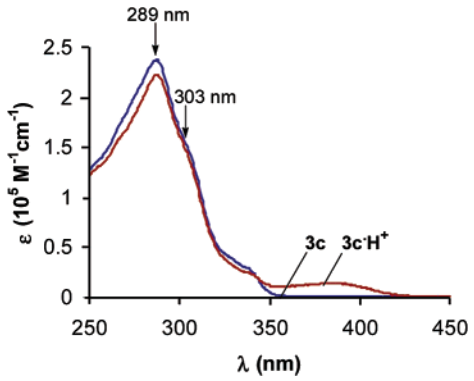


Figure 1. UV spectra of **3c** (blue) and **3c**·H^+ (red) in acetonitrile. The ratio of absorbance bands at 303 and 289 nm changes only minimally upon protonation and indicates a folded conformation for both species. Absorbance at 350−425 nm increases upon protonation, signifying formation of the pyridinium species.

oligomers.[16] The ratio of absorbance bands at 303 and 289 nm for an oligomer in a given solvent is indicative of the predominant conformation of the PE backbone, with low values of $A_{303/289}$ corresponding to a high degree of folding.

Table 1. Yields for Oligomers **2a**−**e** and **3a**−**e**

oligomer	R_1	yield (%)
2a → **5** + **11**	NO_2	41
2b → **9** + **11**	CO_2Me	84
2c → **10** + **11**	H	66
2d → **6** + **11**	OMe	48
2e → **8** + **11**	NMe_2	66
3a → **5** + **12**	NO_2	47
3b → **9** + **12**	CO_2Me	51
3c → **10** + **12**	H	84
3d → **6** + **12**	OMe	51
3e → **8** + **12**	NMe_2	48

The UV spectra of **3** in both unprotonated and protonated forms indicated that the oligomers adopt a helical conformation in acetonitrile (Figure 1), and thus acetonitrile was chosen as the solvent for all pK_a measurements. Measurement of pK_a values in acetonitrile is well documented, with values reported for over 300 compounds.[17] However, the reliability of much of these data is questionable, as values reported by different authors often deviate by more than one pK_a unit.[18] These deviations may arise from difficulties in measuring the acidity of 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 co-workers have recently developed a method for measuring pK_a values in acetonitrile that minimizes these sources of error.[18] This method uses UV−vis spectroscopy to measure ΔpK_a values for sets of compounds having similar aciditities. After measurements have been made for multiple sets of compounds, an acidity scale is constructed on the basis of these 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 ΔpK_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,[19] this method appeared to be suitable for measuring the pK_a values of oligomers **2** and **3**.

In the UV spectra of oligomers **3**, 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 (Figure 1). As a result, acquiring ΔpK_a measurements between oligomers **3** 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. To address this need, a series of azobenzene indicators was developed, and these indicators were used in conjunction with the methods developed by Koppel and co-workers to obtain pK_a values for oligomers **2** and **3** (Table 2).[20]

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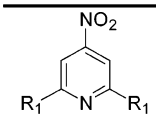
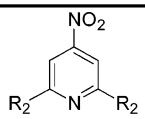
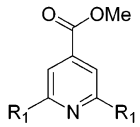
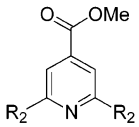
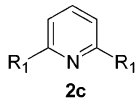
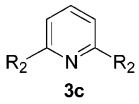
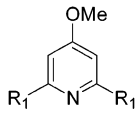
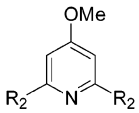
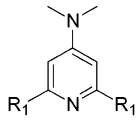
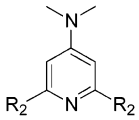
Table 2. pK_a Values of Pyridine-Containing Oligomers

trimers **2a-e**	pK_a[a]	tridecamers **3a-e**	pK_a[a]	$\Delta\Delta G_{protonation}$ (kcal·mol^{-1})
 **2a**	5.4	 **3a**	5.0	-0.5
 **2b**	7.2	 **3b**	7.3	0.1
 **2c**	8.9	 **3c**	8.9	0
 **2d**	10.4	 **3d**	10.4	0
 **2e**	14.0	 **3e**	14.3	0.4

[a] pK_a values are measured in acetonitrile and represent the dissociation constant of the protonated pyridinium ion. All measurements are accurate to ±0.1 pK_a units

The measured oligomer pK_a values reveal that modulating the basicity of the pyridine moiety is, not surprisingly, easily accomplished by changing substituents on the ring, allowing access to a pK_a range of 5−14 in acetonitrile. Folding was also found to have a minor impact on the pK_a values of the oligomers, and unexpectedly, this effect was found to be stabilizing for some oligomers but destabilizing for others. Upon comparing the pK_a values of tridecamers **3** with the corresponding trimers (**2**), it appears that for oligomers having electron-rich pyridine rings, folding stabilizes the pyridinium species, as **3e** is 0.3 pK_a units higher that **2e**, equivalent to a free energy difference ($\Delta\Delta G_{protonation}$) of 0.4 kcal·mol^{-1}. However, for oligomers having electron-poor pyridine rings, folding destabilizes the protonated species, as evidenced by a pK_a difference of −0.4 between **2a** and **3a**, equivalent to a $\Delta\Delta G_{protonation}$ of −0.5 kcal·mol^{-1}.

Changing the substituent on the pyridine ring has little impact on the overall hydrophobicity of the binding cavity, and thus it is unlikely that the local environment of the helical cavity is sufficiently solvent-sheltered to be responsible for the observed shifts in pK_a upon folding. Rather, these changes in pK_a more likely result from pyridinium-π interactions involving the terminal phenyl rings of the oligomers. The electron density of a phenyl ring has been shown to dictate both the sign and intensity of pyridinium-π interactions, with electron-rich phenyl rings stabilizing the pyridinium species and electron-poor phenyl rings having a destabilizing effect.[21] We hypothesize that the electronics of the pyridine ring has an analogous effect, with electron-donating substituents on the pyridine ring giving rise to stabilizing pyridinium-π interactions and electron-withdrawing substituents on the pyridine ring giving rise to destabilizing pyridinium-π interactions. This hypothesis is further supported by the absence of a significant effect of folding on the basicity of oligomers having intermediate pK_a values, as the sign of the pyridinium-π interaction would be expected to change from negative to positive in this range.

In conclusion, the binding cavity of a PE oligomer can be functionalized by incorporation of a basic pyridine moiety. The pK_a values of the oligomers reveal that the basicity of the pyridine nitrogen is easily modulated by changing the substituents on the pyridine ring, allowing access to a broad pK_a range in acetonitrile. Additionally, changes in the local environment of the pyridine ring upon oligomer folding can be used to further modulate the pK_a values of some PE oligomers.

Incorporation of a pyridine functionality having tunable basicity into PE oligomers demonstrates our ability to program information onto the surface of the oligomer binding cavity. This information may be used to direct substrate binding and reaction catalysis, allowing PE oligomers to act as artificial enzymes. Future studies will explore the use of pyridine-contianing oligomers to promote alkylation and acyl transfer reactions.

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Supporting Information Available: Detailed descriptions of all experimental procedures and accompanying analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Details to be published separately: Heemstra, J. M.; Moore, J. S. *Tetrahedron* **2003**, submitted for publication.

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