# Synthesis and Self-Association of an Imine-Containing *m*-Phenylene Ethynylene Macrocycle

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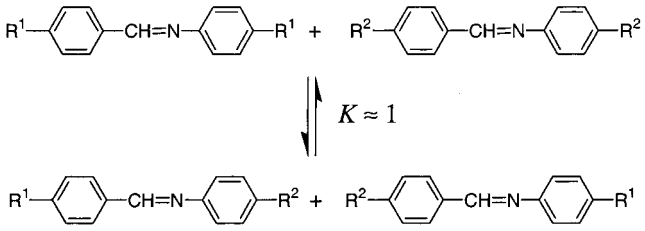
The purpose of this study was to test the suitability of the imine bond as a structural unit within the backbone of phenylene ethynylene macrocycles and oligomers by determining the ability of *m*-phenylene ethynylene macrocycle **1** to form $\pi$-stacked aggregates in both solution and the solid state. Macrocycle **1**, with two imine bonds, was synthesized in high yield from diamine **4** and dialdehyde **5**. The imine-forming macrocyclization step was carried out under a variety of conditions, with the best yield obtained simply by refluxing the reactants in methanol. The self-association behavior of **1** in various solvents was probed by $^1$H NMR. The association constants ($K_E$) in acetone-$d_6$ and tetrahydrofuran-$d_8$ were determined by fitting the concentration-dependent chemical shifts with indefinite self-association models. The results showed that solvophobically driven intermolecular $\pi-\pi$ stacking could be preserved in the imine-containing *m*-phenylene ethynylene macrocycles. Interestingly, in acetone macrocycle **1** exhibited a stronger tendency to form a dimer rather than higher aggregates. We postulate that this behavior may be due to electrostatic attraction between dipolar imine groups. The solid-state packing of **1** was studied by wide- and small-angle X-ray powder diffraction (WAXD and SAXD). Bragg reflections of **1** were consistent with a hexagonal packing motif similar to our previous studies on *m*-phenylene ethynylene macrocycles that formed columnar liquid crystal phases.

## Introduction

The self-organization behavior of a series of discrete *m*-phenylene ethynylene oligomers in solution has been extensively studied in our group.[1] These oligomers collapse into helical conformations in polar solvents and in this conformation are capable of binding nonpolar guests within the tubular cavity.[1a,f,h] It has been previously shown that the folding propensity of the chain, as well as the binding affinity of the helices, are dependent upon the oligomer's chemical structure, chain length, and the solvent.[1] As an extension of these studies, we have begun to embark on a dynamic combinatorial[2,3] approach to synthesize oligo(*m*-phenylene ethynylene)s and thereby identify functional, "masterpiece" sequences.[4] It is conceivable that the population of a copolymer library comprised of oligomers with dynamically diversified chain length and backbone structures could be biased by folding in the presence of certain hydrophobic guests or simply by the folding process itself. To examine this hypothesis, we have chosen a set of *m*-phenylene ethynylene oligomers with imine bonds in the backbone. The reversibly formed imine bond was chosen as the ligation functionality and is envisioned to allow for dynamic sequence diversity (Scheme 1).[5]

**Scheme 1**




The imine bond is more flexible than the ethynylene unit due to its ability to undergo the facile syn−anti isomerization (Scheme 2).[6] The incorporation of the imine bond into the oligomer backbone should diminish the rigidity of the chain by introducing additional conformational freedom. This may result in the decreased stability of the folded conformation for imine-containing oligomers by compromising the $\pi-\pi$ stacking propensity of the backbone and/or increasing the number of conformational

(1) (a) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793. (b) Gin, M. S.; Yokozawa, T.; Prince, R. B.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 2643. (c) Prince, R. B.; Saven, J. G.; Wolynes, P. G.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 3114. (d) Prince, R. B.; Brunsveld, L.; Meijer, E. W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 228. (e) Gin, M. S.; Moore, J. S. *Org. Lett.* **2000**, *2*, 135. (f) Prince, R. B.; Barnes, S. A.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 2758. (g) Brunsveld, L.; Prince, R. B.; Meijer, E. W.; Moore, J. S. *Org. Lett.* **2000**, *2*, 1525. (h) Tanatani, A.; Mio, M. J.; Moore, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 1792. (i) Brunsveld, L.; Meijer, E. W.; Prince, R. B.; Moore, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 7978.

(2) For reviews, see: (a) Ganesan, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2828. (b) Klekota, B.; Miller, B. L. *Trends Biotechnol.* **1999**, *17*, 205. (c) Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455. (d) Cousins, G. R. L.; Poulsen, S.-A.; Sanders, J. K. M. *Curr. Opin. Chem. Biol.* **2000**, *4*, 270.

(3) For recent examples of dynamic combinatorial chemistry, see: (a) Berl. V.; Huc, I.; Lehn, J.-M.; DeCian. A.; Fisher, J. *Eur. J. Org. Chem.* **1999**, 3089. (b) Baxter, P. N. W.; Khoury, R. G.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem. Eur. J.* **2000**, *6*, 4140. (c) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *J. Am. Chem. Soc.* **2000**, *122*, 12063. (d) Furlan, R. L. E.; Cousins, G. R. L.; Sanders, J. K. M. *Chem. Commun.* **2000**, 1761. (e) Star, A.; Goldberg, I.; Fuchs, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 2685.

(4) Moore, J. S.; Zimmerman, N. W. *Org. Lett.* **2000**, *2*, 915.

(5) Tóth, G.; Pintér, I.; Messmer, A. *Tetrahedron Lett.* **1974**, 735.

(6) (a) Padwa, A. *Chem. Rev.* **1977**, *77*, 37. (b) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489.

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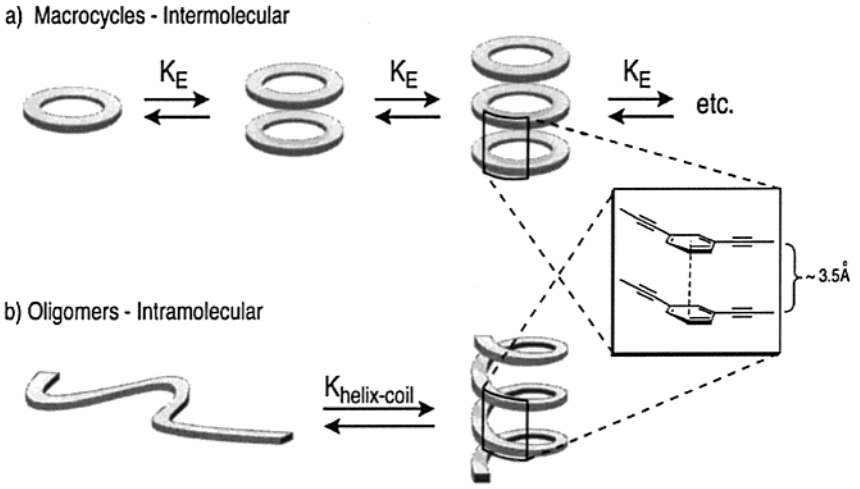
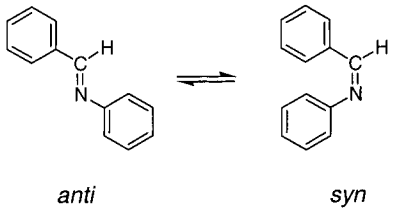



**Figure 1.** Schematic diagram depicting (a) the intermolecular association of macrocycles and (b) the helical conformation of oligo(*m*-phenylene ethynylene)s.

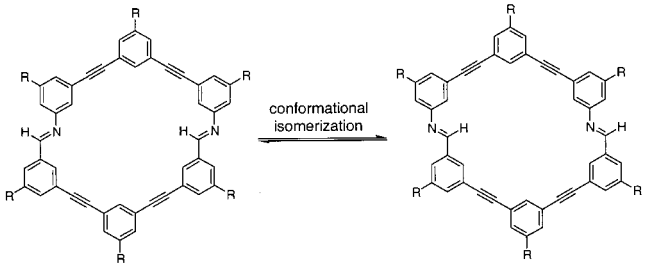
**Scheme 2**



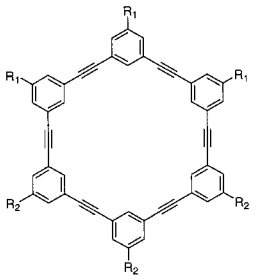

states (i.e., the entropy) of the unfolded state. This article will address the extent to which the incorporation of imine bonds into the backbone may affect the $\pi-\pi$ stacking of phenylene ethynylene oligomers by examining the intermolecular association of the analogous macrocycles.[7]

Previous studies have shown that the stability of the folded helical conformation of *m*-phenylene ethynylene oligomers correlates with the strength of the *inter*molecular association of hexameric macrocycles having the same backbone structure (Figure 1).[7] This observation is best explained by drawing an analogy between a macrocycle and one turn within a helix of the linear oligomer. Hence, macrocycle aggregates may be considered as a model system for the corresponding oligomers in the folded conformation. The *inter*molecular stacking tendency of macrocycles provides a measure of the *intra*molecular folding propensity of oligomers having a similar architecture. Therefore, by comparing the aggregation behavior of the imine-containing macrocycles to macrocycles without imine bonds, we may expect to elucidate the effect of incorporating imine bonds into the *m*-phenylene ethynylene backbone. These results may be extrapolated to predict the stability of helical conformations in imine-containing oligomers. To this end, macrocycle **1** was synthesized and its intermolecular aggregation behavior was investigated and compared with that of macrocycles **2** and **3**, both of which do not contain imine bonds.

Additionally, there has been intense interest in shape-persistent arylene ethynylene macrocycles with respect to their well-defined supramolecular architecture in solution, solid state, and liquid crystalline mesophase.[8,9]




**1** R = $CO_2(CH_2CH_2O)_3CH_3$



**2** $R_1 = R_2 = CO_2(CH_2CH_2O)_3CH_3$
**3** $R_1 = CO_2(CH_2)_5CH_3$
$R_2 = O(CH_2)_5CH_3$

On the other hand, increasing attention has been drawn to macrocycles containing the imine bond as the backbone linkage, either due to their self-assembled cyclic structure by virtue of imine condensation[10] or to their unique double helical motifs upon coordination of transition metals.[11] In view of these interesting potential properties, the synthesis and characterization of **1** by itself is worth pursuing.

(7) Lahiri, S.; Thompson, J. L.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 11315.

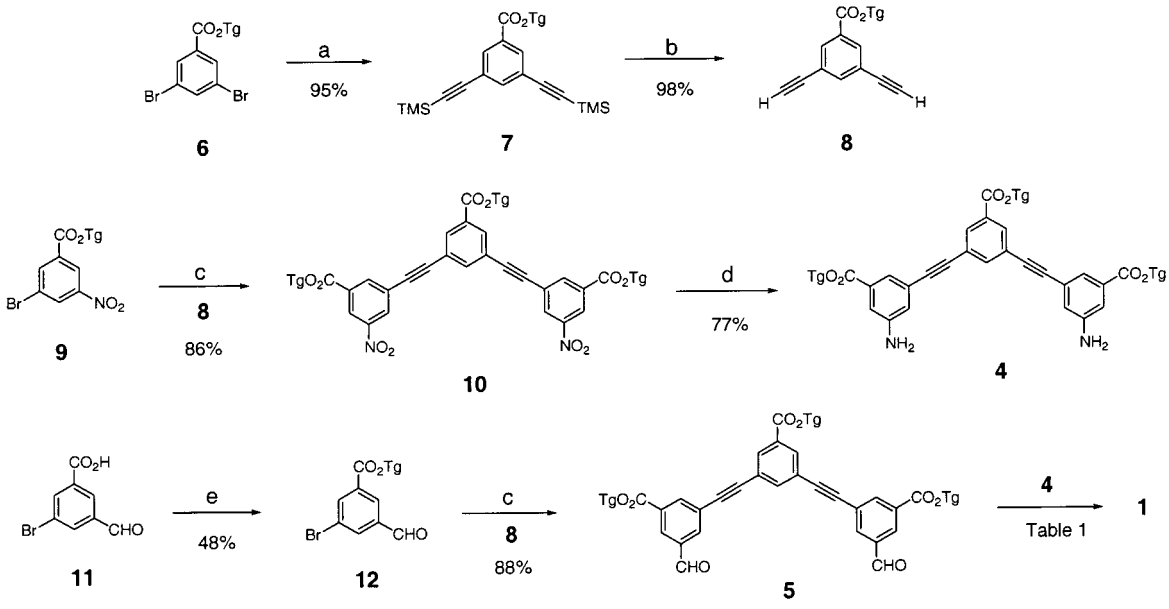
(8) For reviews, see: (a) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (b) Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, *201*, 81.

(9) For recent examples: (a) Höger, S.; Enkelmann, V.; Bonrad, K.; Tschierske, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2268. (b) Henze, O.; Lentz, D.; Schlüter, A. D. *Chem. Eur. J.* **2000**, *6*, 2362. (c) Tobe, Y.; Nagano, A.; Kawabata, K.; Sonoda, M.; Naemura, K. *Org. Lett.* **2000**, *2*, 3265. (d) Nakamura, K.; Okubo, H.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 1097. (e) Höger, S.; Bonrad, K.; Mourran, A.; Beginn, U.; Möller, M. *J. Am Chem. Soc.* **2001**, *123*, 5651.

(10) (a) Higuchi, M.; Kimoto, A.; Shiki, S.; Yamamoto, K. *J. Org. Chem.* **2000**, *65*, 5680. (b) Gawroñski, J.; Kołbon, H.; Kwit, M.; Katrusiak, A. *J. Org. Chem.* **2000**, *65*, 5768.

(11) Comba, P.; Fath, A.; Hambley. T. W.; Kühner, A.; Richens. D. T.; Viefort, A. *Inorg. Chem.* **1998**, *37*, 4389. (b) Fento, D. E.; Matthews, R. W.; McPartlin, M.; Murphy, B. P.; Scowen, I. J.; Tasker, P. A. *J. Chem. Soc., Dalton Trans.* **1996**, 3421.

**Scheme 3**[a]




[a] Reagents and conditions: (a) trimethylsilylethynylene, $Pd_2(dba)_3$, CuI, $PPh_3$, $Et_3N$, 60 °C, 20 h; (b) TBAF, THF, rt; (c) $Pd_2(dba)_3$, CuI, $PPh_3$, $Et_3N$, 70 °C, 36 h; (d) $SnCl_2 \cdot 2H_2O$, EtOH, refluxing, 0.5 h; (e) $CH_3(OCH_2CH_2)_3OH$, DEAD, $PPh_3$, THF, rt. Tg = $(CH_2CH_2O)_3CH_3$.

**Table 1. Conditions for Macrocyclization Reactions**

| solvent | temp | concn, mM | conversion,[b] % |
|---|---|---|---|
| $CDCl_3$ | room temp | 3 | no reacn |
| $CDCl_3$/TFA-*d*[a] | room temp | 3 | <10 |
| toluene | refluxing | 3 | <10 |
| methanol | refluxing | 3 | >95[c] |
| | 90 °C | neat reacn | <60[d] |

[a] Catalytic amount of TFA-*d*. [b] Conversions of amine and aldehyde to imine were calculated on the basis of $^1$H NMR spectroscopy. [c] The yield of **1** after purification by column chromatography was 78%. [d] High molecular weight products were also detected by MALDI-TOF MS and GPC.

## Results

The synthesis of macrocycle **1** is outlined in Scheme 3. The macrocyclization was accomplished through two successive imine condensation reactions between trimeric diamine **4** and dialdehyde **5**.[12] However, the macrocyclization of **4** and **5** was initially not successful under a variety of conditions. When **4** and **5** were reacted under many typical imine-forming conditions (e.g., in chloroform, chloroform with a catalytic amount of trifluoroacetic acid, or refluxing toluene), the overall conversion of aldehyde and amine to imine was below 10% based on the $^1$H NMR spectra of the resulting mixtures (Table 1). In contrast, a high yield of macrocycle **1** was obtained by refluxing stoichiometric amounts of **4** and **5** in methanol for 20 h. A $^1$H NMR spectrum of the crude product showed that conversion to macrocycle **1** had proceeded to over 95% completion, with no observable side products. Under these conditions no oligomeric products of a molecular weight higher than that of macrocycle **1** were detected by MALDI-TOF MS, even when the stoichiometry of **4** and **5** was not strictly controlled. In contrast, under neat reaction conditions wherein the premixed **4** and **5** were heated at 90 °C in vacuo for 12 h in the absence of any solvent, a mixture of **1** and higher molecular weight oligomers was formed (MW ranging from about 2600 to 13 000 as measured by MALDI-TOF MS and GPC). The yield of macrocycle **1** under these solventless conditions was less than 60% on the basis of $^1$H NMR integration.

Macrocycle **1** exhibited good solubility in a variety of solvents and good solution stability in the absence of water. No aldehyde or amine protons were detected by $^1$H NMR when the spectrum of **1** was recorded in chloroform, tetrahydrofuran (THF), acetonitrile, or dimethyl sulfoxide (DMSO) solution for 3 days. Only a trace amount of the imine was hydrolyzed into aldehyde and amine after the sample was exposed to air for 3 months. However, the imine bond was labile in the presence of water; when **1** was kept in a DMSO-$d_6$/$D_2O$ (1:1) solution for 3 days, over 80% of the imine bonds were hydrolyzed as shown by the $^1$H NMR spectrum.

The aggregation behavior of macrocycle **1** was investigated by $^1$H NMR spectroscopy. The spectra of **1** were recorded at room temperature in a series of solvents (Figure 2). Eleven distinct resonances were observed in aromatic region of spectra recorded in $CDCl_3$ and THF-$d_8$ at room temperature. At constant concentration with increasing solvent polarity, pronounced upfield shifting and resonance broadening were observed for the aromatic protons and the imine proton (−C*H*═N−, $\delta$ = 8.69 ppm in $CDCl_3$). The magnitude of upfielding shifting and resonance broadening correlated with increasing polarity of the solvent.

Besides solvent polarity, the chemical shifts of the aromatic protons and the imine proton were also sensitive to the concentration of the macrocycle. In a given solvent, as the concentration of **1** increased, similar upfield shifting and resonance broadening was observed. The chemical shifts of the aromatic protons and the imine proton were measured at room temperature as a function of concentrations in acetone-$d_6$ (Figure 3) and THF-$d_8$ (Figure 4).[13] The data were first analyzed using a

(12) Reversible imine formation and exchange reactions have been described with other systems: (a) Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363. (b) Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1913. (c) Ro, S.; Rowan, S. J.; Pease, A. R.; Cram, D. J.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 2411.

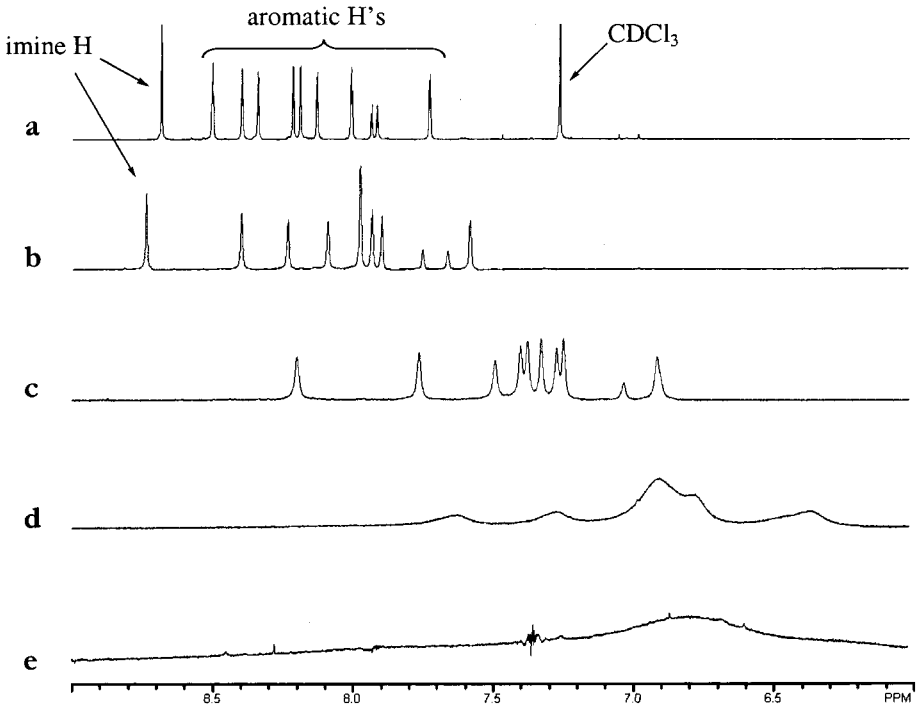



**Figure 2.** Aromatic region of $^1$H NMR spectra (500 MHz) of **1**, at room temperature and a concentration of 3 mM, in a series of solvents: (a) $CDCl_3$, (b) THF-$d_8$, (c) acetone-$d_6$, (d) $CD_3CN$, and (e) DMSO-$d_6$.

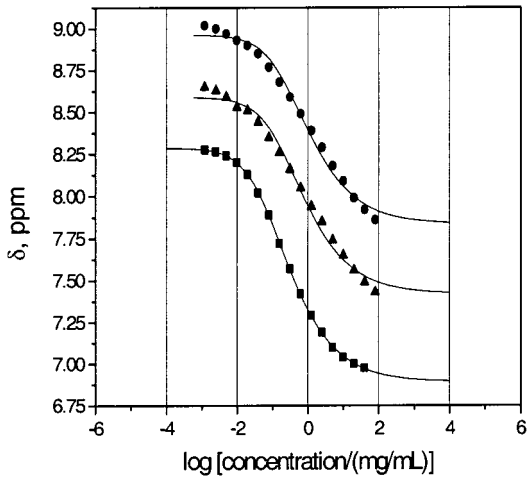



**Figure 3.** Plot of chemical shift vs log [concentration/(mg/mL)] in acetone-$d_6$ at room temperature (●, imine H of **1**; ▲, aromatic H of **1**; ■, aromatic H of **2**). The curves represent the best fit of the experimental data to the isodesmic model of indefinite association.

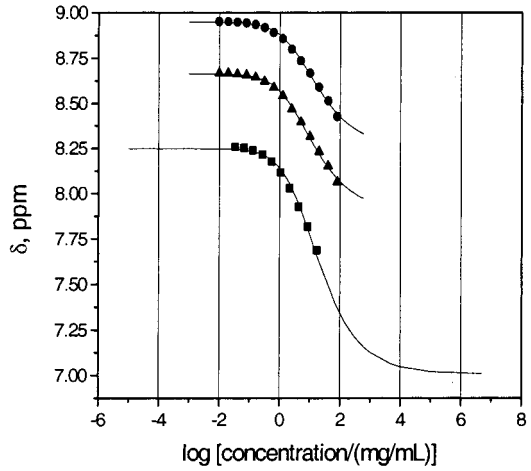



**Figure 4.** Plot of chemical shift vs log [concentration/(mg/mL)] in THF-$d_8$ (●, imine H of **1**; ▲, aromatic H of **1**; ■, aromatic H of **2** as previously reported).[7] The curves represent the best fit of the experimental data to the isodesmic model of indefinite association.

nonlinear least-squares regression analysis in Mathematica 3.0 and then fitted to an equation derived from the isodesmic model of indefinite association.[14,15] In this model it is assumed that the free energy, and thus the association constant $K_E$, for successive addition of each macrocycle to an aggregate (or another single macrocycle) is identical (equal $K$ model). Using the same method as previously described,[7] the association constants ($K_E$) of **1** in these two solvents at room temperature were determined (Table 2). It is apparent from Figure 3 that the chemical shift data obtained with acetone-$d_6$ did not fit the equal $K$ model very well, so a modification to the model was applied in which the association constant for dimerization ($K_2$) was allowed to differ from the association constants for forming higher aggregates ($K_E'$). The $^1$H NMR data were simulated and fitted by nonlinear least-squares regression analysis using the computer program Dynafit.[16] Using the refined model, a better fit

(13) For previously studied macrocycle **2**, over the concentration range available for $^1$H NMR experiments, the largest chemical shift change was observed in acetone-$d_6$ with a modest change in THF-$d_8$. Therefore, acetone-$d_6$ and THF-$d_8$ were chosen as the solvents to quantitatively compare the association constants of **1** to those of **2** and investigate the effect of the imine bond on $\pi-\pi$ stacking.

(14) Martin, R. B. *Chem. Rev.* **1996**, *96*, 3043.

(15) $P = P_{monomer} - \Delta(1 + (1 - (4K_E c_t + 1)^{1/2})/(2K_E c_t))$ ($P$ is the observed chemical shift, $P_{monomer}$ is the chemical shift of monomer, $K_E$ is the association constant, $c_t$ is the molar concentration of the macrocycle, and $\Delta$ is the chemical shift difference between monomer and dimer).

(16) The program Dynafit: Kuzmič, P. *Anal. Biochem.* **1996**, *237*, 260.

**Table 2. Association Constants ($K_E$) of Macrocycles 1 and 2**

| | $K_E$ ($M^{-1}$) | | |
|---|---|---|---|
| | **1** | | |
| solvent | imine H[a] | aromatic H[b] | **2**[c] |
| acetone-$d_6$ | 3600 ± 1300 | 4800 ± 1800 | 13 000 |
| THF-$d_8$ | 220 ± 40 | 290 ± 50 | 350 |

[a] Calculated $K_E$ of **1** on the basis of the chemical shift of imine H. [b] Calculated $K_E$ of **1** on the basis of the chemical shift of aromatic H. [c] Previously reported $K_E$ of **2**.[7]

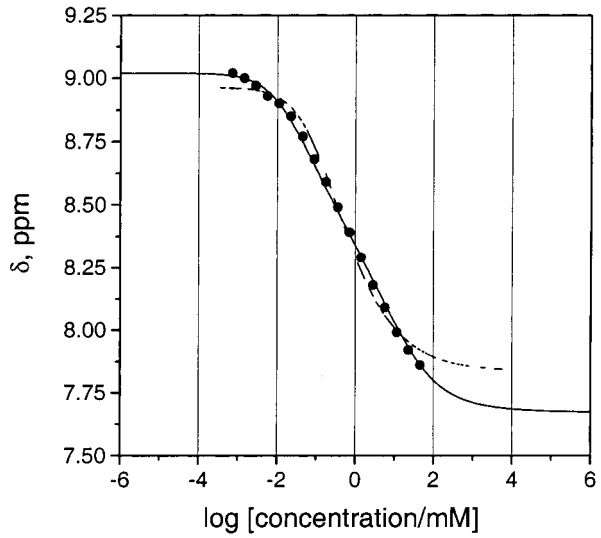



**Figure 5.** Plot of chemical shift vs log [concentration/mM] in acetone-$d_6$ (●, imine H of **1**). The solid curve (—) represents the best fit of the experimental data to the modified isodesmic model of indefinite association ($K_2$ = 12 700 ± 1100 $M^{-1}$, $K_E'$ = 2570 ± 440 $M^{-1}$) and the dashed curve (– - –) represents the best fit to the isodesmic model ($K_E$ = 3600 ± 1300 $M^{-1}$).

was obtained (Figure 5). The best fits of $K_2$ and $K_E'$ based on the chemical shifts of imine proton in acetone-$d_6$ solution were 12 700 and 2570 $M^{-1}$, respectively.

In addition to the concentration study on macrocycle **1**, a variable temperature (VT) $^1$H NMR study was also conducted in $CD_2Cl_2$. The purpose of this study was to examine the possibility of a dynamic process such as the conformational isomerism shown along with the chemical structure of **1**. Upfield shifting and broadening of the aromatic and imine proton resonances was observed as the temperature was lowered from +20 to −50 °C. Thus we are not able to conclude if conformational isomerism is slowing down at low temperature.

UV−vis absorbance spectra of macrocycle **1** were recorded in chloroform and acetonitrile at a concentration of 2.0 × $10^{-5}$ M. Only one dominant absorbance band with a $\lambda_{max}$ at ca. 290 nm was observed for **1** independent of the solvent utilized, while two distinct $\lambda_{max}$ were observed for the open chain trimeric precursor **5** (Figure 6). This is consistent with the all-*cisoid* state of the cyclic phenylene ethynylene backbone of **1**.[1a]

Macrocycle **1** is an off-white, waxy solid at room temperature. Although no discernible phase transition was identified by differential scanning calorimetry (DSC) between −100 and +200 °C, **1** showed strong birefringence under plane polarized light. The birefringence persisted upon heating from 25 to 270 °C, where **1** began to decompose. In addition, the solid-state packing of **1** was probed by X-ray powder diffraction. The X-ray

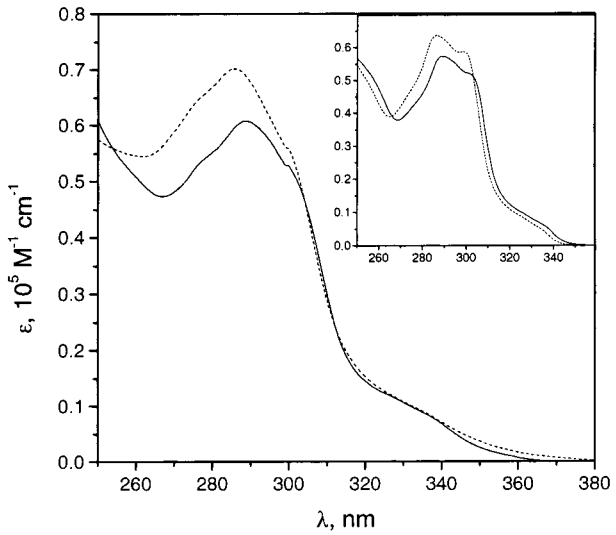



**Figure 6.** UV−vis spectra of **1** in chloroform (—) and acetonitrile (– - –) at a concentration of 2.0 × $10^{-5}$ M. The inset shows the UV−vis spectra of **5** in the same solvents with two absorbance bands at ca. 290 and 300 nm, corresponding to the *cisoid* and *transoid* states of the oligo(*m*-phenylene ethynylene) unit, respectively.

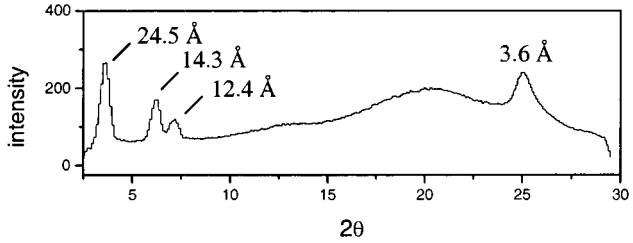



**Figure 7.** WAXD profile of macrocycle **1** at room temperature.

**Table 3. X-ray Powder Diffraction Data of 1**

| *d*-spacing (Å) | | |
|---|---|---|
| obs | calcd[a] | corresponding to |
| 3.6 | | aromatic stacking |
| 4.4 | | side chain interdigitation |
| 12.4 | 12.3 | hexagonal lattice (200) |
| 14.3 | 14.1 | hexagonal lattice (110) |
| 24.5 | 24.5 | hexagonal lattice (100) |

[a] Based on hexagonal lattice with a lattice parameter $a$ = 28.3 Å.

samples were prepared using a solvent-evaporation method previously described.[17] Wide- and small-angle X-ray diffraction (WAXD and SAXD) profiles of **1** were collected at room temperature (Figure 7). The *d*-spacing data derived from WAXD Bragg reflections are listed in Table 3. The SAXD profile gave one peak corresponding to a *d*-spacing value of 25.0 Å, in agreement with the lowest angle reflection observed by WAXD.

## Discussion

Although the cyclic structure of **1** precludes the syn conformation of the imine bond, a concerted rotation around the relatively flexible phenylene−imine−phenylene linkage would allow the macrocycle to experience a double inversion, that is, to isomerize between two equivalent conformers assuming that a nearly planar

(17) Mio, M. J.; Prince, R. B.; Moore, J. S.; Kuebel, C.; Martin, D. C. *J. Am. Chem. Soc.* **2000**, *122*, 6134.

conformation is the most stable state. Many of the conformational states occurring during this inversion process would not be planar, possibly compromising the stacking ability of the macrocycle. This would result in the observed decreased self-association constant of **1** relative to **2.** Macrocycles experiencing nonplanar conformations would be expected to have a diminished stacking propensity.[14] The $^1$H NMR spectra were carefully examined to investigate these potential conformational dynamics. Since only 11 distinct aromatic resonances, including that of the imine proton, were observed for macrocycle **1** at room temperature, it is suggested that this crankshaft-like rotation was occurring rapidly in solution on the NMR time scale. To investigate the time scale of this interconversion, variable temperature $^1$H NMR experiments were conducted in $CD_2Cl_2$. At low temperatures, it was thought that the macrococyle might become locked in a planar conformation, resulting in some of the aromatic resonances splitting due to the differentiated chemical environments of the protons. Unfortunately, aggregation was observed as the temperature was decreased, as evidenced by the upfield shifting and line broadening of the resonances. It was thus not possible to verify the existence of the isolated planar macrocyclic conformation.

Upfield shifting in $^1$H NMR spectra has been well-documented as a signature of aromatic stacking interactions.[14,18] Previously in our laboratory it was demonstrated that macrocycles **2** and **3**, both of which have been proven by vapor pressure osmometry to form intermolecular aggregates in solution, experienced significant upfield shifting of their aromatic protons in polar solvents.[7,19] This indicated that the $\pi-\pi$ stacking interaction between phenylene ethynylene units is sensitive to solvent polarity. $^1$H NMR spectra of macrocycle **1** displayed a similar solvent dependent upfield shifting and resonance broadening, indicating that the macrocycle was aggregating in solution and that the extent of self-association was dependent upon the solvent polarity.[20] The chemical shifts of **1** in a given solvent were also sensitive to the macrocycle concentration, consistent with increased intermolecular aggregation at higher concentration.

The association constants obtained from the nonlinear least-squares regression analysis in Mathematica were fairly large (Table 2). Although the association constants of **1** were smaller compared to those of macrocycle **2** in the same solvent,[7] the significant absolute values of $K_E$ indicated that aggregation was occurring. Thus, the most important conclusion is that imine bond does not severely disrupt $\pi$-stacking. Surprisingly, although the $^1$H NMR results of **1** in THF and macrocycle **2** in both acetone and THF are well-described by the isodesmic model, a good fit using this model could not be obtained for macrocycle **1** in acetone (Figure 3). This suggested that a different type of self-association was being exhibited by **1** in acetone, and thus a different model would be needed.

Previous reports have suggested that a modification to the isodesmic model, in which the association constant of dimerization ($K_2$) is allowed to vary from the subsequent higher order association constants (i.e., all subsequent $K_E'$s, which are assumed to be equal), may provide a viable alternative when the isodesmic model fails.[14] In this new model, a $K_2$ larger than $K_E'$ represents a tight dimerization followed by weaker isodesmic association to form higher aggregates. On the other hand, a smaller $K_2$ indicates a disfavored dimerization followed by stronger isodesmic association (essentially cooperative aggregation). Our efforts to fit the chemical shift data of **1** in acetone-$d_6$ solution to this alternative model using the program Dynafit[16] gave better agreement of the data to the new model over the entire range of concentration that was studied (Figure 5). Interestingly, the best fit $K_2$ (12 700 $M^{-1}$) was approximately 5 times larger than $K_E'$ (2570 $M^{-1}$). Although there have been reports of systems which exhibit a $K_2$ larger than $K_E'$ [14] none of these systems have demonstrated such a significant magnitude of difference between $K_2$ and $K_E'$ when both $K_2$ and $K_E'$ have substantial absolute values.

For neutral molecules without a significant steric hindrance, like our macrocycle, a $K_2$ smaller than $K_E'$ is usually expected and predominantly observed.[14] This may be attributed to the extra entropy expense involved in dimerization. On the other hand, when $K_2$ is found to be larger than $K_E$, steric hindrance related to further association to the dimeric form or electrostatic repulsion in charged molecules have been postulated as possible reasons why a smaller $K_E'$ is observed.[14] However, neither of these explanations satisfied our system here. A new rational explanation was needed to account for the peculiar, nonintuitive self-association behavior of macrocycle **1**. As previously demonstrated in our laboratory, macrocycle **2** with a backbone exclusively composed of phenylene ethynylene units followed the self-association behavior predicted by the isodesmic model. The only structural difference between macrocycles **1** and **2** is that a pair of ethynylene units in **2** have been replaced by polar imine bonds in **1**. Along with this structural change, a dipole moment is introduced into the originally apolar framework.[21] A pair of macrocycles with dipole moments within their skeleton may prefer to orient in a certain direction relative to each other when dimerizing, most likely stacking in an antiparallel orientation with regard to the $-CH=N-$ units (Figure 8). If this hypothesis is valid, the symmetry of the dimer would diminish or even eliminate the charge separation, leading to the observed weakness of the higher order association following the tight dimerization.[20,22]

Our previous studies on macrocycle **3**, which has a disc-shaped backbone and alkyl side chains, exhibited an

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(20) Imine units brought into close vicinity of one another in dimeric form may facilitate the imine metathesis/exchange reaction as shown in Scheme 1. However, according to ref 5, we do not expect the reaction to take place at an observed rate under the conditions of the NMR experiments. Moreover, when macrocycle **1**, at a concentration of 5 mM in $CD_3CN$ where **1** is proven to form aggregates, was treated with catalytic amount of acid, the conditions under which the imine metathesis/exchange reaction has been both reported[5] and proven by our independent study to proceed properly at room temperature, no higher molecular weight product was observed by MALDI-TOF mass spectroscopy. The high stability of **1** may result from the optimal planar conformation of the hexameric macrocycle for aggregation.

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(22) Results from crystallographic data search on aromatic imines from the Cambridge Structural Database (CSD) supported out hypothesis by showing that in the solid state aromatic imines exhibit a preference to be aligned with phenyl rings intermolecularly stacked face-to-face and imine units oriented antiparallel with respect to one another.

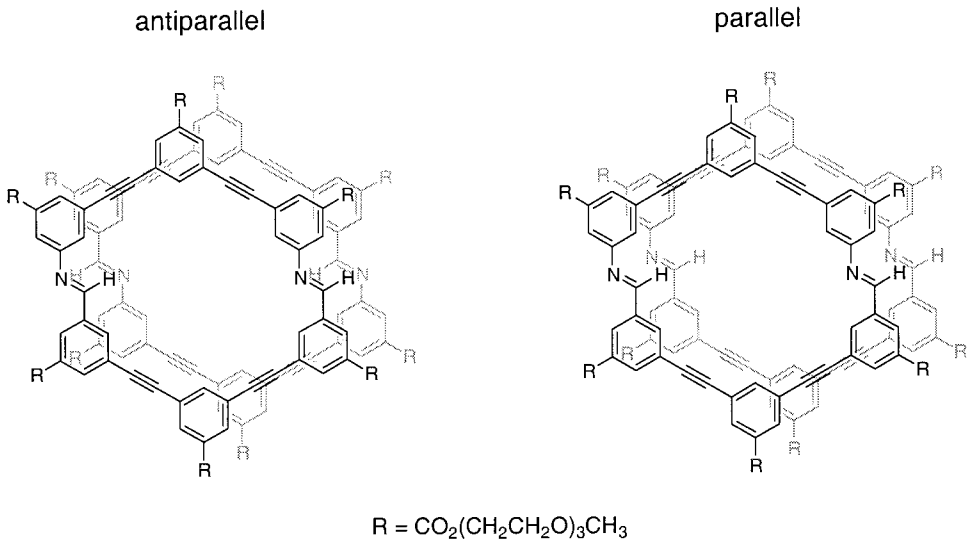


**Figure 8.** Representative stacking orientation of macrocycle **1** in a dimer (left, antiparallel orientation; right, parallel orientation).

ordered columnar mesophase with a slightly offset hexagonal packing.[23,24] As macrocycles **1** and **3** have similar backbone structures, and $^1$H NMR studies have shown that the imine bond did not preclude the intermolecular association of the macrocycle in solution, ordered columnar architectures were also considered to be possible for macrocycle **1** in the solid state. The strong birefringence shown by **1** when examined under the polarized optical microscope supported the existence of mesophase order.

More conclusive evidence for an ordered solid-state structure came from the X-ray powder diffraction studies. In the WAXD profile of **1**, a reflection with a *d*-spacing corresponding to the stacking of the macrocycle (3.6 Å) confirmed that the macrocycles were face-to-face in the solid state and suggested that the aromatic interaction was still effective after incorporating the imine bond into the backbone. Although there is evidence suggesting that **1** undergoes conformational isomerization (crankshaft-like motion) in solution due to the flexibility of the imine linkage, the presence of the 3.6 Å *d*-spacing of the ring-to-ring distance within a stack, suggests that **1** is forced to take up a nearly planar conformation when packed in the solid state. Presumably this is the case for solution aggregates too. The reflections in the WAXD profile, with *d*-spacing values of 24, 14, 12, and 3.6 Å (Table 3), were also in good agreement with the reflections observed for **3**.[23,24] The ratio of the first three of these *d*-spacing values (1:1/$\sqrt{3}$:1/2) index to a hexagonal lattice. These observations indicate that **1** exhibits a hexagonally packed columnar structure at room temperature.

## Conclusions

*m*-Phenylene ethynylene macrocycle **1** with two imine bonds in its backbone has been synthesized and characterized. The intermolecular $\pi-\pi$ stacking and association ability of macrocycle **1** in solution were probed by $^1$H NMR, and it was shown that **1** formed aggregates in solution and exhibited a favored dimer formation process followed by weakened strength in the subsequent association steps to form higher aggregates. The dipole moment present in this imine-containing phenylene ethynylene macrocycle was proposed to be responsible for the uncommon self-association, and the enhanced strength of dimerization could be derived from an electrostatic (dipole−dipole) interaction between the two monomeric components. In the solid state, WAXD and SAXD manifested columnar structures of face-to-face stacked macrocycle **1** packed in a hexagonal lattice, indicating that in the solid state a nearly planar disc-like shape was conserved in **1**.

The self-association behavior exhibited by **1** in both solution and the solid state suggests that the imine bond is compatible with the *m*-phenylene ethynylene system and does not significantly interfere with $\pi-\pi$ stacking interactions. Therefore, this functionality is anticipated to serve as a suitable reversible ligating group enabling exchange or metathesis reactions among *m*-phenylene ethynylene oligomers of various lengths and backbone structures in order to realize the function-driven synthesis of "masterpiece" sequences. These studies are under investigation in our laboratory and will be reported in due course. The interesting self-association behavior of the macrocycle has also lead us to envision controllable adjustment of the association strength and folding stability of phenylene ethynylene oligomers by manipulating the orientation of the imine units in the backbone through sequence design.

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**Supporting Information Available:** Text describing the syntheses and NMR and MS data of **4**−**12** and **1** and the method used to fit $^1$H NMR data to the nonequal *K* model. This material is available via the Internet at http://pubs.acs.org.

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