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Macrocycles

Synthesis of Phenylene Vinylene Macrocycles through Acyclic Diene Metathesis Macrocyclization and Their Aggregation Behavior

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Abstract: A series of phenylene vinylene macrocycles (PVMs) bearing substituents with various sizes and electronic properties have been synthesized through a one-step acyclic diene metathesis macrocyclization approach and their aggregation behaviors have been investigated. In great contrast to the aggregation of the analogous phenylene ethynylene macrocycles, which aggregate only when substituted with electron-withdrawing groups, these PVMs undergo exceptionally strong aggregation, regardless of the electron-donating or -withdrawing characters of the substituents. The unusual aggregation behavior of the PVMs is further investigated with thermodynamic and computer modeling studies, which show a good agreement with the recently proposed direct through-space interaction model, rather than the polar/π model. The high aggregation tendency of PVMs suggests the great potential of this novel class of shape-persistent macrocycles in a variety of applications, such as ion channels, host–guest recognition, and catalysis.

Introduction

Shape-persistent macrocycles (SPMs) have attracted considerable attention due to their self-aggregation behavior and unusual electronic and optoelectronic properties.[1–5] These molecules have rigid non-collapsible backbone structures and can assemble into supramolecular systems, such as perforated monolayers and discotic liquid crystalline materials.[6] Among the numerous SPMs, arylene ethynylene macrocycles (AEMs) are the most widely studied and many interesting applications based on AEMs have emerged.[7–14] Recent advances in dynamic covalent chemistry,[15–17] namely alkyne metathesis, have enabled the facile access to AEMs on gram scale, and boosted the applications of these macrocycles toward materials development.[18–20]

It has been reported that the self-association of AEMs is induced by face-to-face π–π interactions between aromatic rings and is strongly influenced by the rigidity of the backbone structures and pendant functional groups of the macrocycles: Electron-withdrawing substituents promote self-aggregation of macrocycles, whereas electron-donating functional groups have the opposite effect; a planar and rigid framework enhances the aggregation, whereas a flexible nonplanar geometry inhibits it.[21,22] These experimental results are interpreted by the well-known polar/π model, which predicts the substituent effects based on the polarization of the π system.[23–26]

Arylene vinylene macrocycles (AVMs) are structural analogues of AEMs, in which arylenes are connected by carbon–carbon double bonds with trigonal planar geometry rather than linear triple bonds. However, AVMs are uncommon and their supramolecular properties have rarely been explored. One such example was reported by Meier and co-workers. They synthesized various areno-condensed annulenes connected by *E*-vinylene bridges through a multistep synthetic approach and showed that these macrocyclic annulenes can aggregate and serve as photoconductors and discotic mesogens.[27–29] Recently, our group developed a high-yielding acyclic diene metathesis macrocyclization (ADMAC) approach to form AVMs from simple precursors in one step.[30] Our preliminary study shows that AVMs containing carbazole-vinylene or phenylene-vinylene groups easily aggregate and form nanofibrils. More interestingly, the hexa(phenylvinylene) macrocycle substituted with electron-donating alkoxy groups also shows strong self-association in $CDCl_3$. It is in great contrast to the non-aggregation character of analogous hexa(phenylethynylene) macrocycle with alkoxy substituents under the same solvent, and thus surprising, especially considering the skeletal flexibility and lower rigidity of AVMs arising from the possible conformational isomerism of vinylene moieties.

To better understand the unusual aggregation behavior of AVMs, herein, we report the design and synthesis of a series of phenylene vinylene macrocycles (PVMs) bearing various side chains of different sizes and electronic natures and investigated their aggregation. We found that PVMs aggregate regard-

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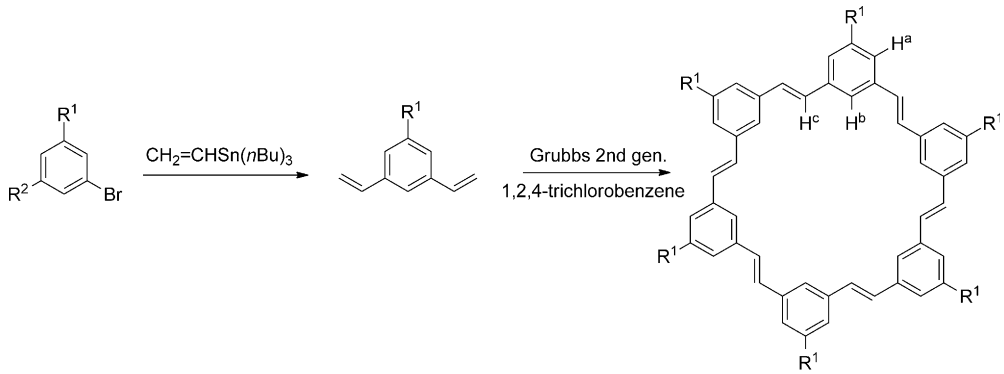
less of whether they contain electron-withdrawing or electron-donating substituents. Such peculiar substituent effects cannot be readily explained by the polar/π model, but agree well with the recently proposed direct through-space interaction model.[31–40] Our thermodynamic and computer modelling studies further support such a theory, which emphasizes substituent effects on π-stacking are due to direct interactions of the substituents with the neighboring π-system rather than polarization of the aryl π-system.

Results and Discussion

Synthesis of PVMs

Divinylbenzene monomers **9**–**16**, with various electronically and sterically different substituents, were prepared from dihalobenzenes **1**–**8** (halogen = Br or I) by Stille coupling reactions



1: $R^1 = nC_{10}H_{21}$; R^2 =Br
2: $R^1 = tC_4H_9$; R^2 =Br
3: $R^1 = OnC_{10}H_{21}$; R^2 =Br
4: $R^1 = OnC_4H_9$ R^2=Br
5: $R^1 = OCOnC_9H_{19}$; R^2 =Br
6: $R^1 = COOnC_{10}H_{21}$; R^2 =I
7: $R^1 = COOnC_4H_9$; R^2 =I
8: $R^1 = COOtC_4H_9$; R^2 =I

9: $R^1 = nC_{10}H_{21}$ (67%)
10: $R^1 = tC_4H_9$ (69%)
11: $R^1 = OnC_{10}H_{21}$ (59%)
12: $R^1 = OnC_4H_9$ (73%)
13: $R^1 = OCOnC_9H_{19}$ (84%)
14: $R^1 = COOnC_{10}H_{21}$ (57%)
15: $R^1 = COOnC_4H_9$ (47%)
16: $R^1 = COOtC_4H_9$ (85%)

17: $R^1 = nC_{10}H_{21}$ (54%)
18: $R^1 = tC_4H_9$ (65%)
19: $R^1 = OnC_{10}H_{21}$ (64%)
20: $R^1 = OnC_4H_9$ (74%)
21: $R^1 = OCOnC_9H_{19}$ (51%)
22: $R^1 = COOnC_{10}H_{21}$ (45%)
23: $R^1 = COOnC_4H_9$ (74%)
24: $R^1 = COOtBu$ (47%)

Scheme 1. Synthesis of PVMs through ADMAC.

(Scheme 1). The crude yields of Stille coupling are generally above 90% based on the NMR analyses of the crude reaction mixtures. However, considerably lower yields (50–70%) could be isolated, mainly due to (1) the low stability of the divinyl monomers, which easily polymerize in the solid state and in air within several hours to form waxy insoluble polymers, and (2) extensive purification. The excess tributyl(vinyl)tin and tributyltin chloride byproducts often have similar polarities to those of the products (e.g., **9**–**12**) and their removal requires repetitive column chromatography purification.

PVMs **17**–**24** were prepared through thermodynamically-controlled one-step ADMAC approach using Grubbs' second generation catalyst at 40 °C under nitrogen. In all cases, cyclic hexamers were obtained as the predominant species with various amounts of cyclic heptamer and cyclic pentamer as minor species (see the Supporting Information, Figure S9). Theoretical calculations confirm that the formation of hexameric PVMs over pentameric or heptameric PVMs is thermodynamically favored (see the Supporting Information, Table S1). Pure cyclic hexamers **17**–**24** were isolated in decent yields (45–74%) through repeated careful column chromatography. This synthetic protocol is thus modular and allows for the cyclooligomerization of a variety of monomer units with differing substituents in a straightforward manner.

All PVMs were characterized by ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF MS. We observed two sets of broad singlets corresponding to the protons on the phenyl ring. The vinyl protons of the PVMs appeared as a singlet in the ^{1}H NMR spectra, both at room temperature and at 0 °C. This chemical shift equivalence suggests the two seemingly different vinyl protons, located inside and outside of the macrocyclic ring, are interchangeable through the rapid rotational isomerization of the double bonds.

Self-association of PVMs

We next investigated the self-association behaviors of various PVMs and compared them with those of the analogous phenylene ethynylene macrocycles (PEMs). The concentration- and temperature-dependent aggregation of PVMs was studied with ^{1}H NMR spectroscopy (Figure 1). To minimize the solvophobic effect on the aggregation, we used deuterated chloroform, in which PVMs readily dissolve, as the solvent in all aggregation experiments. With increased concentration or decreased temperature, the aromatic proton (H^a and H^b) and vinyl proton (H^c) peaks were shifted upfield. Such shielding effects on PVMs are

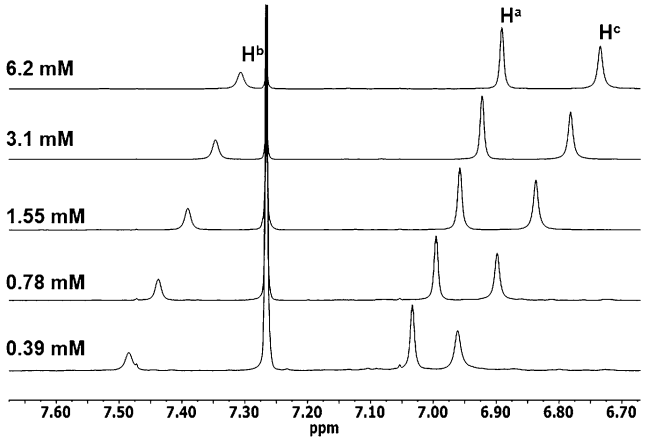


Figure 1. ^{1}H NMR spectra of PVM **21** at various concentrations. ^{1}H NMR spectra were recorded in $CDCl_3$ at 296 K.

similar in trend, albeit much more significant, compared to the cases of PEMs. Interestingly, the aggregation properties of PVMs are strongly influenced by the polarity of substituents and whether the functional groups can donate or withdraw electron density from the macrocyclic core appears less important. Pronounced concentration-dependent ^{1}H NMR chemical shift changes were observed for PVMs **19**–**23** with either electron-donating or -withdrawing substituents (Figure 2), but not

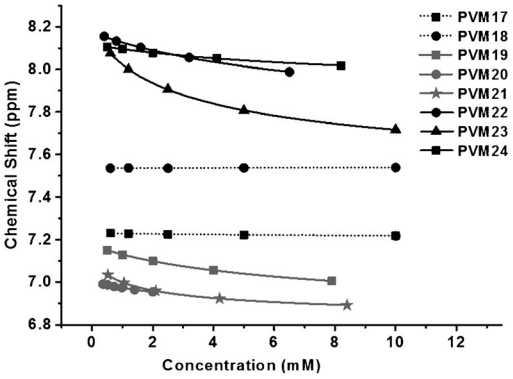


Figure 2. The concentration-dependent chemical shifts of *exo*-annular protons (H^a) of PVMs **17**–**24**. ^{1}H NMR spectra were recorded in $CDCl_3$ at 296 K.

for PVMs **17** and **18**, containing nonpolar alkyl substituents. At ambient temperature, the chemical shift of two anisochronous aromatic protons of PVM **21** (R = OCO*n*C_9H_{19}) changed from 7.49 ppm to 7.31 ppm and from 7.03 ppm to 6.89 ppm respectively, as the concentration was increased from 0.39 to 6.2 mM (Figure 1). The changes in the chemical shift of *exo*-annular (H^a) and *endo*-annular (H^b) protons were similar in both trend and magnitude for the same PVM. The chemical shifts of aliphatic protons remain unchanged over the same concentration range. The aggregation behaviors of PVMs are also temperature dependent. When the temperature was raised, the resonance peaks of *exo*-annular and *endo*-annular protons of PVM **21** were shifted to lower field, which indicates that dissociation occurs at elevated temperature (see the Supporting Information, Table S7 and Figure S12).

The aggregation of PVMs in solution was also studied by fluorescence spectroscopy. We observed significant fluorescence quenching in the solution of PVM **23** when the solvent was changed from chloroform to acetonitrile. However, such fluorescence quenching behavior was absent in the emission spectra of non-aggregating PVM **18** under the same experimental conditions (see the Supporting Information, Figure S11). These results further suggest the fluorescence quenching observed for PVM **23** is attributed to its aggregation.

To further quantify the self-association constants, we first estimated the size of macrocycle aggregates from the diffusion coefficient of the stacked species in solution. The diffusion coefficient was obtained through diffusion-ordered spectroscopy (DOSY) experiments. We used PVM **21** and PVM **23**, which show the strongest aggregation, as the representative examples to estimate the number of macrocycles per stacked species. We assume that PVM **21** and PVM **23** are present as monomeric species at the lowest studied concentration (0.13 mM, and 0.66 mM, respectively). Our study (for details, see the Supporting Information) shows that the number of aggregates of both PVM **21** and PVM **23** are around two at the highest studied concentration (4.08 mM and 10.5 mM, respectively). Therefore, it is mainly monomer–dimer aggregation that occurs and formation of higher order aggregates beyond dimers is insignificant in the concentration range we studied for PVM **21** and **23**. We assume that the aggregations of other PVMs (**19**, **20**, **22**, **24**), which show weaker self-association in $CDCl_3$ than **21** and **23**, are mainly limited to dimerization.

Since DOSY experiments support monomer–dimer equilibrium as the major aggregation process, the concentration-dependent chemical shift data of *endo*- and *exo*-annular protons of PVMs were analyzed by using the monomer–dimer model [Eq. (1)][41]

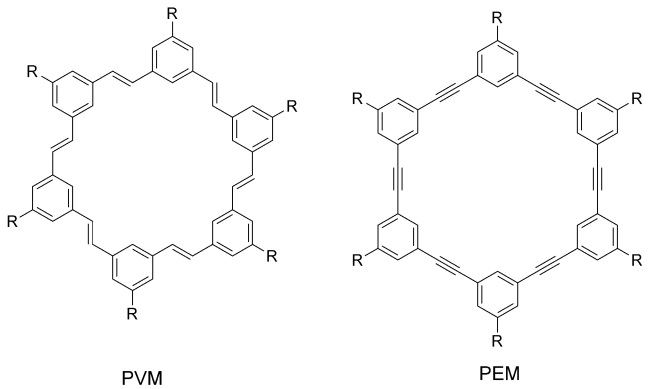
$$\delta_{obs} = \delta_{monomer} - \Delta\left(1 + \frac{(1 - \sqrt{8K_{assoc}c_t + 1})}{4K_{assoc}c_t}\right) \quad (1)$$

where δ_{obs} is the observed chemical shift, $\delta_{monomer}$ is the chemical shift of the monomer, K_{assoc} is the association constant, c_t is the molar concentration of the PVM, and Δ is the chemical shift difference between monomer and dimer. Self-association constants of PVMs were then extracted by using nonlinear least-squares regression method from the concentration-dependent chemical shifts of *exo*-annular (H^a) and the *endo*-annular (H^b) protons of PVMs at 296 K. We were able to identify the best values of association constants, which give the smallest standard deviations in the curve fitting, for macrocycles showing significant aggregation (see the Supporting Information, Figures S15–S18). The self-association constants calculated from *endo*- and *exo*-annular protons of the PVMs are in good agreement, within experimental error. PVM **21**, functionalized with "reverse" ester (OCO*n*C_9H_{19}), gave the strongest self-association constants (Table 1). We also observed strong aggregation of PVMs **20** (R = O*n*C_4H_9) and **23** (R = COO*n*C_4H_9). Surprisingly, PVM **24**, substituted with *tert*-butyl ester, also underwent decent aggregation, although K_{assoc} was decreased four-fold compared to that of PVM **23**, substituted with *n*-butyl esters. The length of alkyl chains attached to the ether or ester groups negatively influenced the aggregation of PVMs, likely due to the larger entropic loss upon aggregation. We observed much stronger aggregation of PVMs **20** (R = O*n*C_4H_9) and **23** (R = COO*n*C_4H_9) compared to PVMs **19** (R = O*n*$C_{10}H_{21}$) and **22** (R = COO*n*$C_{10}H_{21}$), respectively.

Substituent effects

Previously, Moore and co-workers reported that PEMs undergo considerable aggregation only when functionalized with electron-withdrawing groups (e.g., COO*n*C_4H_9), and no obvious aggregation when functionalized with electron-donating groups (e.g., O*n*C_4H_9; Table 1). This is in good agreement with the polar/π model,[26] which predicts that the introduction of electron-withdrawing substituents reduces the electron density of

Table 1. Thermodynamic data of self-association of PVMs (296 K) and PEMs (293 K) in $CDCl_3$.



R (PVM)	K_{assoc} [M^{-1}]	R (PEM)[45]	K_{assoc} [M^{-1}]
$nC_{10}H_{21}$(PVM **17**)	<5	$CH_2OnC_4H_9$	≈ 0
tC_4H_9 (PVM **18**)	≈ 0		
$OnC_{10}H_{21}$ (PVM **19**)	60		
OnC_4H_9 (PVM **20**)	99	OnC_4H_9	≈ 0
$OCOnC_9H_{19}$ (PVM **21**)	628	$OCOnC_4H_9$	≈ 0
$COOnC_{10}H_{21}$ (PVM **22**)	45		
$COOnC_4H_9$ (PVM **23**)	168	$COOnC_4H_9$(PEM **25**)	60
$COO^tC_4H_9$ (PVM **24**)	40	$COO^tC_4H_9$	≈ 0

the π-system and thus decreases the electrostatic repulsion between π electrons and promotes π-stacking. However, the aggregation properties of PVMs appear to be independent on the electron-withdrawing or -donating nature of the substituents. This is in striking contrast to the aggregation behaviors of PEMs and appears to be in contradiction to the polar/π model. Similar substituent effects to our results were recently reported by Swager and Houk for stereoselective Diels–Alder cycloadditions, showing that -OMe enhances π-stacking interactions, despite its π-electron donating character.[40] Gas-phase ab initio computations by Sherrill and co-workers also revealed enhanced stacking interactions in the sandwich benzene dimer, regardless of the electron-withdrawing or electron-donating character of the substituents.[37–39] More recently, Houk and Wheeler highlighted the direct through-space interaction model, in which the substituent effects correlate with σ_m, not σ_p, the inductive/field effects of the substituents rather than π-polarization.[33–36] Although large aromatic systems (e.g., macrocyclic rings) might be different from the more-studied smaller aromatics, our results agree well with this direct through-space interaction model, which predicts that π-donating but σ-withdrawing alkoxy substituents will enhance stacking interactions.

On the basis of the aforementioned models for substituent effects in stacking interactions, these PVMs present themselves as appealing direct experimental evidence for the emerging direct through-space interaction model. To further corroborate the theory, we first investigated the thermodynamics of the aggregation process of PVMs. For ease of comparison, we chose to use PVM **23**, substituted with $COOnC_4H_9$, as a representative model compound, for which the $T\Delta S$ and ΔH values of self-association can be readily compared to the literature values of analogous PEM substituted with the same functional groups (i.e., PEM **25**). The thermodynamic parameters of the aggregation process of PVM **23** were obtained through variable-temperature NMR experiments (see the Supporting Information, Figure S13) and subsequent Van't Hoff analysis (Figure S14). The thermodynamic study showed that the aggregation of PVM **23** occurs with comparable enthalpy gain ($\Delta H = 4.9$ kcal mol^{-1} vs. 5.0 kcal mol^{-1}) as PEM **25** but with a smaller entropy loss ($\Delta S = -6.2$ cal $mol^{-1} K^{-1}$ vs. -9.2 cal $mol^{-1} K^{-1}$). These results can be readily explained by the direct through-space interaction model, in which the substituents directly interact with the neighboring macrocycle's π-system. In such a model, the position of the substituents can directly influence the magnitude of stacking interactions, as reported by Gung and co-workers.[42] In PVMs, the optimal conformation to maximize stacking interactions can be easily achieved due to the additional conformational flexibility arising from the rotational freedom of vinylene groups. On the contrary, it would be more difficult for rigid PEMs to achieve the optimal stacked conformation, leading to increased entropic penalties.

The exceptionally high degree of self-aggregation of PVM **21** substituted with "reverse" ester is intriguing, considering that the electronic effect of the "reverse" ester is between that of the electron-donating alkyl ether and that of the electron-withdrawing alkyl ester group. To gain some insight into this interesting observation, we modeled the PVM **21** structure by using density functional theory (DFT) calculations by Gaussian 09.[43] The dimer structure of PVM **21** was optimized by using the B3LYP method with the 6-31G* basis set. It should be noted that there may exist various conformational isomers as a result of the rotation of vinylene groups. The most stable conformer with C_6 symmetry was used in the calculation as the monomer structure. The energy- minimized dimer structure of PVM **21** (Figure 3) adopts a geometry that is off-set by 30°

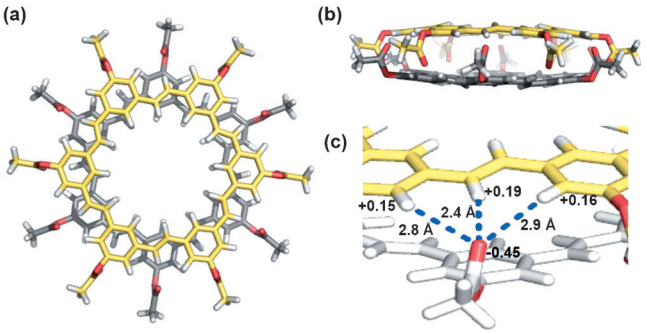


Figure 3. Energy-minimized structure of PVM 21 dimer: a) Top view; b) side view; c) expanded view.

around the principle rotational axis of macrocycles. Interestingly, upon dimerization, PVMs deviate from the perfectly planar conformation to the slightly puckered form, where the macrocycles bend towards one another, presumably to reach maximum direct through-space interaction between the substituents and the π-system of the neighboring macrocycle. In addition, the "reverse" ester groups on the periphery of the macrocycle are in close contact with the vinylene protons of the

neighboring ring. We found strong electrostatic interactions between the negatively charged carbonyl oxygen (Mulliken partial atomic charge = −0.45) and one positively charged vinylene hydrogen (+0.19) as well as two positively charged phenyl hydrogens (+0.15 and +0.16), with the total positive charge on the all three hydrogens of +0.50. These hydrogen atoms are in the close proximity of the carbonyl oxygen with the distances of 2.4 Å, 2.8 Å and 2.9 Å, respectively (Figure 3c). This result also agrees with the previous report by Rashkin and Waters, which described a similar direct electrostatic interaction of the edge hydrogens of one ring with electronegative substituents on the other ring.[44] However, we did not observe a downfield shift of the vinyl protons of PVM **21** upon aggregation. Instead, we observed an upfield shift of those protons, indicating that the shielding effect of macrocyclic ring current overshadows the deshielding effect from the electrostatic interaction. Considering the complexity of the large macrocyclic ring system, the exceptionally high aggregation tendency could be due to the combination of multiple interactions, including π-stacking, electrostatic, and solvophobic interactions.

Conclusion

A series of phenylene vinylene macrocycles were successfully synthesized through thermodynamically-controlled one-step ADMAC approach from simple diene monomers. The synthetic protocol is modular and straightforward, allowing for a variety of monomer units with differing substituents to be cyclized. The aggregation behaviors of these PVMs were systematically studied. ^{1}H NMR DOSY experiments supported a predominant monomer–dimer equilibrium during the aggregation process rather than the formation of higher oligomers. Based on the "monomer–dimer" model, the self-association constants were calculated from the concentration dependent NMR chemical shift data of the PVMs. Despite of their structural similarity, PVMs exhibit much stronger aggregation tendency compared to the analogous PEMs. More interestingly, PVMs aggregate even when they are substituted with electron-donating groups. Our results can be explained by the new direct through-space interaction model of π-stacking interactions, rather than the polar/π model. The thermodynamic study on the aggregation of PVM and PEM with the same substituents indicates that PVM gains comparable enthalpy but loses smaller entropy during the aggregation, which is likely due to the increased conformational freedom of PVMs. Computer modeling studies suggested the possible direct through-space electrostatic interaction between the substituents and peripheral hydrogen atoms as the additional driving force for the strong aggregation of PVMs. These results provide experimental and theoretical support for the recently proposed model of π-stacking interactions, which argues that direct interactions of the substituent with the neighboring π-system dominate the substituent effects, rather than π-polarization. Our study will nicely complement the current structure design and synthetic approaches for shape-persistent macrocyclic compounds and provides more insight into how their aggregation can be manipulated by altering the backbone structures, as well as side-chain substituents.

Experimental Section

Typical ADMAC procedure: To a Schlenk tube were added divinyl monomer (0.055 mmol) and a solution of Grubbs' 2nd generation catalyst (0.0055 mmol) in 1,2,4-trichlorobenzene (1 mL). The reaction apparatus was evacuated and refilled with nitrogen and this process was repeated three times. The solution was heated at 40 °C under nitrogen for 18 h. Upon completion of the reaction, all solvent was removed and diethyl ether (10 mL) was added. The ethereal solution was washed with water (3×10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (eluent: CH_2Cl_2/hexanes or EtOAc/hexanes) afforded the pure product.

Acknowledgements

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Keywords: aggregation · dynamic covalent chemistry · macrocycles · olefin metathesis · π interactions

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