JOC Article

Theoretical Study of Helix Formation in Substituted Phenylene Ethynylene Oligomers

Richard A. Blatchly*,† and Gregory N. Tew*,‡

Chemistry Department, Keene State College, Keene, New Hampshire 03435, and Polymer Science and Engineering, University of Massachusetts, 120 Governors Dr., Amherst, Massachusetts 01002

rblatchly@keene.edu; tew@mail.pse.umass.edu

Received June 13, 2003

Theoretical investigations of the relative stabilities of helical vs extended forms of phenylene ethynylene oligomers established that MMFF molecular mechanics was more useful than AM1 or DFT for calculating helical structures and for estimating relative energies. At the level of MMFF, theory predicts that for *o*- or *m*-oligophenylene ethynylenes, helix formation is enthalpically favored for ester and ether-substituted oligomers. In contrast to simple electron-demand predictions, we predict that the position of substituents can make a substantial difference in the tendency to form helices.

Introduction

Foldamers have captured the attention of many research groups over the past decade.[1−7] Nonetheless, the field is still in its infancy with design rules available for only a few of the many possible molecular backbones. Phenylene ethynylene (PE) oligomers are an important class of these compounds due to their ease of synthesis, compatibility with a variety of substituents, and relatively well-characterized folding reaction. Both the *m*- and the *o*-PEs are capable of forming a helical structure with 6 and 3 rings per turn, respectively.[8,9] Of the two isomers, *m*-PEs have been studied more thoroughly[9−14] than ortho isomers for their helical propensity. Qualitatively, the basic forces driving the extended to helix transition, or folding reaction, should be the same for each system. These are thought to be mainly $\pi-\pi$ stacking[9,15] and solvophobic interactions.[9,10] In addition, helix formation should require some loss of entropy and the balance of favorable folding energies vs entropy loss will impact helix stability. As part of a much larger program, we wanted to evaluate the ability of computational methods to provide insight on the helix-stabilizing forces that balance the required lower entropy of the folded conformations. Experimentally, there are a number of parameters to investigate; however, improved computational methods allow more rapid insight and quicker production of structural variants than does the wet laboratory.

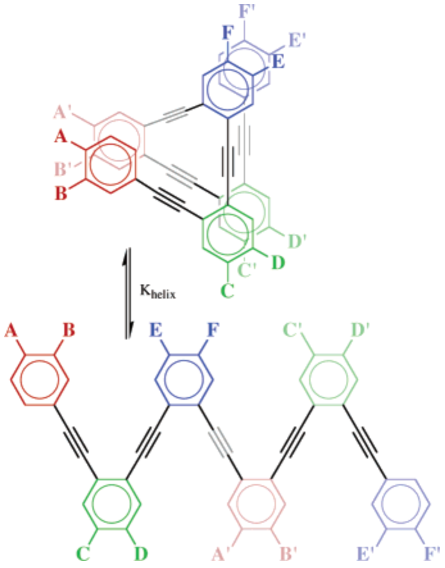

FIGURE 1. Helix-forming reaction of *o*-phenylene ethynylenes (*o*-PE).

The transition between extended and helical forms of the two PE isomers (Figures 1 and 2) is a simple

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† Keene State College.

‡ University of Massachusetts.

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10.1021/jo034827y CCC: $25.00

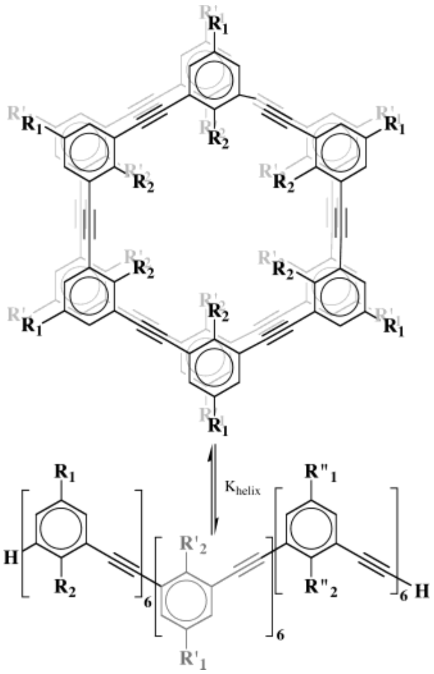


FIGURE 2. Helix-forming reaction of *m*-phenylene ethynylenes (*m*-PE).

unimolecular transition especially well suited for modeling, which allows us to calculate ΔH_{helix} values ($H_{\text{helix}} - H_{\text{extended}}$). The free energy of folding is represented in eqs 1 and 2 for two different oligomers of the same class (meta or ortho). The values obtained from computation allow us to compare different oligomers and obtain $\Delta\Delta H$ values for comparison. Although ΔH values are not perfectly comparable to ΔG, they can make a useful approximation, allowing us to evaluate the effects structural changes have on the folding equilibrium. No experimental measurements of ΔS_{helix} are reported for comparison. However, the value of ΔS for a related dimerization of macrocycles is negative;[16] but even for the dimerization it does not outweigh ΔH at room temperature. As a result, we have not evaluated entropic effects.

$$\mathrm{A}_{\text{extended}} \rightleftharpoons \mathrm{A}_{\text{helix}} \qquad \Delta G_{\mathrm{A}} = \Delta H_{\mathrm{A}} - T\Delta S_{\mathrm{A}} \tag{1}$$

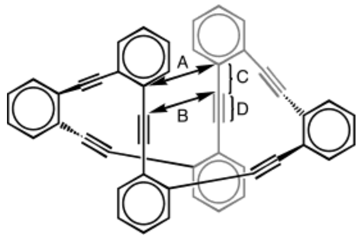
$$\mathrm{B}_{\text{extended}} \rightleftharpoons \mathrm{B}_{\text{helix}} \qquad \Delta G_{\mathrm{B}} = \Delta H_{\mathrm{B}} - T\Delta S_{\mathrm{B}} \tag{2}$$

$$\Delta\Delta G = \Delta G_{\mathrm{B}} - \Delta G_{\mathrm{A}} \tag{3}$$

Results and Discussion

(a) Validation. An extremely important consideration for any computational program is to determine the level of theory needed to provide useful predictions. Therefore, validation of our theoretical system and choice of theory level was performed in three separate series of experiments by comparing computational results with those of solid-state crystal structures, solution equilibrium studies, and theoretical work. Due to the complexity of some molecules (mostly size), we were unable to examine all levels of theory, but did perform structure minimizations using three different levels of theory in initial cases. We focused our exploration to the MMFF molecular mechanics system,[17,18] AM1 semiempirical methods, and DFT ab initio methods, each available in Spartan.[19]

TABLE 1. Comparison of Minimized Cyclic Hexamer Structures to X-ray Crystal Structure



	X-ray	MMFF	AM1	DFT
A	3.54	3.84	4.23	4.34
B	3.36	3.84	4.28	4.28
C	1.426	1.432	1.405	1.418
D	1.201	1.201	1.200	1.225

[a] Interatomic distances *A* and *B* and bond lengths *C* and *D* are in Å.

Initial validation experiments were performed on the solid-state crystal structure of the cyclic PE6 (shown with Table 1), which is the most relevant structure in the CSD.[20] Comparison of models minimized by all three levels of theory provided the pleasantly surprising result that the least costly technique was also the best at predicting the structure. While none of the minimized models matched the crystal structure perfectly, MMFF performed the best by only slightly overestimating inter-ring distances and accurately calculating bond lengths. By contrast, AM1 overestimated inter-ring distances and underestimated the single-bond C−C distances while DFT calculations also overestimate ring distances and triple bond lengths, but underestimate the C−C single bond length. Although these results are important, solution conformation predictions are of more interest here.

Therefore, we tested two helical systems based on *m*-PE structures for which quantitative free energy values have been published.[9,21] A set of molecules with and without methyl groups located in the cavity of the helix, as shown in Figure 2 ($R_2 = R'_2 =$ Me or H), provide an excellent case study because of the very conservative mutation. Solution experimental evidence[21] indicated an increased stability for the methylated helix over the proton derivative by approximately 0.35 kcal/mol per methyl group, while modeling results determined an increased stability of 0.5 kcal/mol per methyl group over the proton derivative. The similarity between experimental and computational values is suggestive that computational methods can provide useful guidance for PE oligomers. As was the case with the crystal structure, modeling with AM1 predicted neither the correct energies nor the correct geometry, proposing interlayer distances

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[19] Wavefunction, Inc.

[20] Cambridge Structural Database

[21] Prince, R. B.; Barnes, S. A.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 2758−2762.

TABLE 2. Helix Formation in Substituted *m*-Phenylene Ethynylene Oligomers

oligomer	R_1	R_1'	R_1''	ΔG_{helix}[a]	ΔH_{helix}[b]
1	CO_2CH_3	CO_2CH_3	CO_2CH_3	−7.5	−89.5
2	CO_2CH_3	CH_2OCH_3	CO_2CH_3	−2.5	−84.0
3	OCH_3	OCH_3	OCH_3	>0	−67.6
4	H	H	H		−47.9

[a] Experimental value[15] (kcal/mol). [b] Calculated value (MMFF, kcal/mol).

of ∼8 Å instead of ∼4 Å. These results strongly suggest the MMFF level of theory can provide useful trends and was therefore chosen for future work.

Next, the ability of theory to predict relative energies of molecules with more widely different substituents was explored in a series of three *m*-PEs with ester, ether, and benzyl ether side chain functions. When MMFF was used, helix stability was predicted to follow the experimentally determined order[15] (ester > benzyl ether > ether) despite simplified side chains,[22] which is consistent with classic $\pi-\pi$ stacking arguments.[23,24] Although electron demand arguments based on classical $\pi-\pi$ stacking would suggest the alternating ester−ether helix should be more stable than the homo ester,[23−25] experiments and calculations shown in Table 2 showed that oligomers with alternating ester and benzyl ether layers (**2**) were less stable than the homo ester (**1**), while being more stable than the homo benzyl ether (not shown).[15] While strict comparison of experimental values for ΔG and computational values for ΔH is not possible, it is worth noting that the trends agree completely ($\Delta\Delta H = 5$ kcal/mol for oligomers **1** and **2**). Calculations at the AM1 level failed to predict any difference between these systems. We have not attempted to calculate entropy for these equilibria, but consider all computational results in light of this omission. We also note that the calculations do not include solvent, which is an important consideration that we plan to address in future work.

Finally, we compared our system to another theoretical study that calculated ΔH_{helix} values for a series of unsubstituted *o*- and *m*-PEs by using very high level ab initio theory.[26] The ΔH_{helix} calculated by this computationally expensive level of theory for *o*-PEs was quite similar to that calculated by MMFF, as shown in Figure 3. The slopes of the two lines are identical for the two different levels of theory, which provides further confidence in MMFF to make useful predictions of PE oligomers. In addition, MMFF allows the practical study of much larger molecules than does ab initio theory as shown in Figure 3.

(b) Application of Theory to New Systems. Once validation showed the ability of MMFF to give reasonable insight into PE structures, we turned to the design of prospective synthetic targets, which is the ultimate use for computational modeling in our laboratories. Inspired by Iverson's aedemer approach[25,27−29] and our interest in *o*-PEs,[30] we turned to modeling a series of *o*-PEs with both electron-rich (ether) and electron-poor (ester or cyano) substituents. We chose to model three substitution patterns on the *o*-PE system. The results of four modeled patterns are presented and will be referred to as "di", "stacked", "Alt1", and "Alt2" forms as shown in Figure 4. These correspond with Figure 1 in which the substituents are located at positions ABCDEF and A′B′C′D′E′F′ or some combination of these positions.[31] In addition, Table 3 summarizes the variety of substituents investigated, which are referenced to the labeled positions shown in Figure 1.

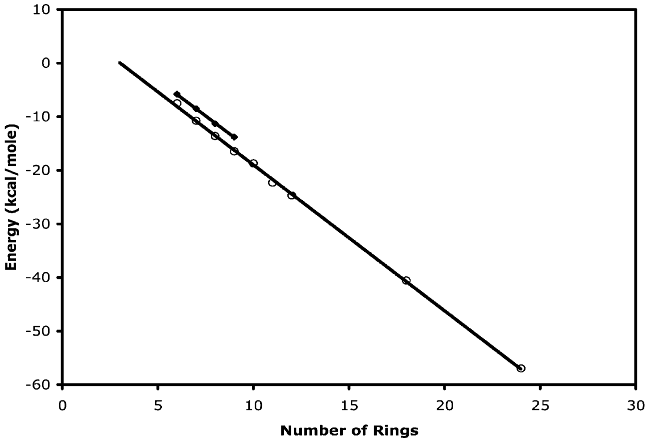

FIGURE 3. Formation energies (ΔH_{helix}) of unsubstituted *o*-phenylene ethynylene oligomers. Open circles are MMFF energies (slope = −2.72), and solid diamonds are ab initio values[26] (slope = −2.68).

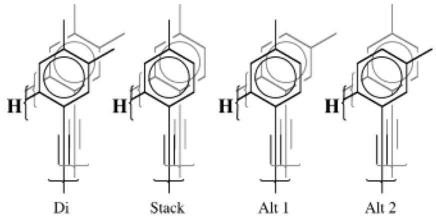

FIGURE 4. Substitution patterns for *o*-PE hexamers.

As the series evolved, molecules with rigid, cyclic substituents were included to provide more clarity into the relative interlayer orientation of side chain functions upon helix formation.

Initial results comparing unsubstituted hexamer **5** and substituted compounds **6**, **7**, and **8** were found to conflict with a simple electron-demand argument based on clas-

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[22] Calculations were performed on systems identical with the experimental oligomers except for end groups and side chains. Methyl side chains were used in place of the experimental tetraglycol.

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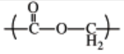
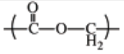
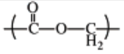
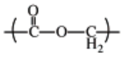
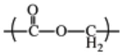
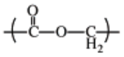
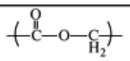
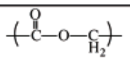
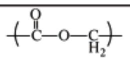
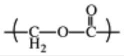
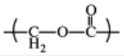
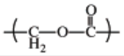
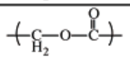
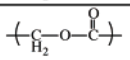
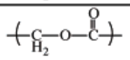
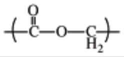
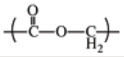
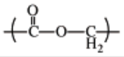
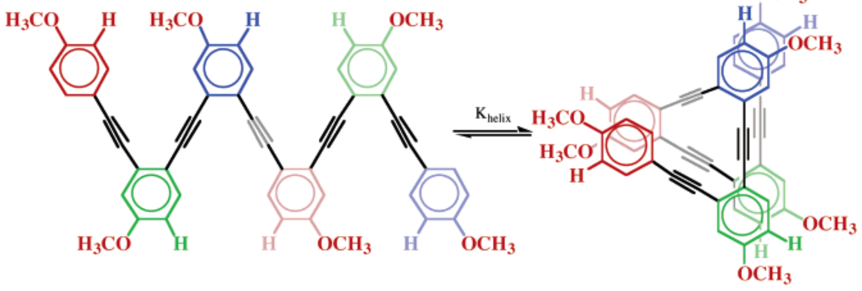
[31] The C2 symmetry equates the stacked form ACEA′C′E′ with BDFB′D′F′. There are two alternating forms, one with substituents at ACEB′D′F′ (which we arbitrarily called Alt1), and one with substituents at BDFA′C′E′ (Alt2). The oPE helix naturally adopts an offset stack geometry in which the center of a ring in one layer is approximately 1.5 Å off the center of a ring in the subsequent layer. This asymmetry causes the interaction between A and B′ to be different from that between A′ and B. In the Alt1 helix, the substituents should be closer together than in the Alt2 helix.

TABLE 3. Helix Stabilization Energies (kcal/mol) for Substituted *o*-PE Hexamers Calculated with MMFF

Cmpd[a]	Layer[b]	A	B	C	D	E	F	H_{ext}	H_{helix}	$-\Delta H_{helix}$
5	1	H	H	H	H	H	H	116.5	109.0	7.5
	2	H	H	H	H	H	H			
6	1	OMe	OMe	OMe	OMe	OMe	OMe	219.9	203.4	16.5[c]
	2	OMe	OMe	OMe	OMe	OMe	OMe			
7	1	OMe	CN	OMe	CN	OMe	CN	175	154	21.0
	2	CN	OMe	CN	OMe	CN	OMe			
8	1	CN	CN	CN	CN	CN	CN			8.0[d]
	2	CN	CN	CN	CN	CN	CN			
9a	1	OMe	H	OMe	H	OMe	H	122.9	109.2	13.7
	2	OMe	H	OMe	H	OMe	H			
9b	1	OMe	H	OMe	H	OMe	H	126.3	113.9	12.1
	2	H	OMe	H	OMe	H	OMe			
9c	1	H	OMe	H	OMe	H	OMe	119.9	107.9	12.0
	2	OMe	H	OMe	H	OMe	H			
10	1	CO_2Me	CO_2Me	CO_2Me	CO_2Me	CO_2Me	CO_2Me	78.5	64.8	13.7
	2	CO_2Me	CO_2Me	CO_2Me	CO_2Me	CO_2Me	CO_2Me			
11a	1	CO_2Me	H	CO_2Me	H	CO_2Me	H	161.5	145.3	16.2
	2	CO_2Me	H	CO_2Me	H	CO_2Me	H			
11b	1	CO_2Me	H	CO_2Me	H	CO_2Me	H	168.7	153.5	13.2
	2	H	CO_2Me	H	CO_2Me	H	CO_2Me			
11c	1	H	CO_2Me	H	CO_2Me	H	CO_2Me	152.8	138.3	14.5
	2	CO_2Me	H	CO_2Me	H	CO_2Me	H			
12a	1	 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		144.0	137.4	6.6
	2	 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$				
12b	1	 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		153.6	135.7	17.9
	2	 $\left(\underset{H_2}{C}-O-\overset{O}{\overset{\|}{C}}\right)$		 $\left(\underset{H_2}{C}-O-\overset{O}{\overset{\|}{C}}\right)$		 $\left(\underset{H_2}{C}-O-\overset{O}{\overset{\|}{C}}\right)$				
12c	1	 $\left(\underset{H_2}{C}-O-\overset{O}{\overset{\|}{C}}\right)$		 $\left(\underset{H_2}{C}-O-\overset{O}{\overset{\|}{C}}\right)$		 $\left(\underset{H_2}{C}-O-\overset{O}{\overset{\|}{C}}\right)$		136.7	120.4	16.3
	2	 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$		 $\left(\overset{O}{\overset{\|}{C}}-O-\underset{H_2}{C}\right)$				
13	1	$-O-CH_2-O-$	$-O-CH_2-O-$	$-O-CH_2-O-$	$-O-CH_2-O-$	$-O-CH_2-O-$	$-O-CH_2-O-$	93.7	79.6	14.1
	2	$-O-CH_2-O-$	$-O-CH_2-O-$	$-O-CH_2-O-$	$-O-CH_2-O-$	$-O-CH_2-O-$	$-O-CH_2-O-$			
14a	1	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	145.0	132.2	12.8
	2	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$			
14b	1	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	146.9	131.5	15.4
	2	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$			
14c	1	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$	$-(CH_2)_2-O-$	144.5	129.0	15.5
	2	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$	$-O-(CH_2)_2-$			

[a] Example structure for compound 9b:



[b] Layer corresponds to the helix layer in the hexamer; substituents in column A, layer 2 are in the A′ position, according to Figure 1. [c] The perfectly eclipsed all syn helix (see Figure 5) has an H_{helix} value of 206.6 kcal/mol. [d] The helix is misshapen or poorly formed, as judged by inter-ring distances (significantly over 4 Å).

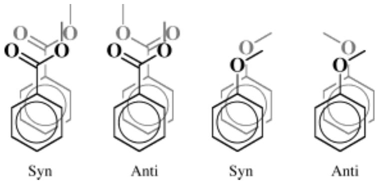


FIGURE 5. Syn vs anti interlayer conformations: calculations predict the anti conformation to be lower in energy as expected.

sical $\pi-\pi$ stacking, which suggests that the most favorable helix should come from molecules bearing a layer of electron-rich rings alternating with a layer of electron-poor rings, followed by structures with only electron-withdrawing substituents.[23,25] Finally, electron-rich rings should have the lowest stabilizations of all,[15] perhaps not even enough to overcome the loss of entropy on helix formation, or favoring edge-on conformations[24] which would likely not help helix formation. For example, the helix determined by modeling to be most stable, **7**, has electron-rich rings stacked on electron-poor rings consistent with $\pi-\pi$ arguments. However, contrary to these arguments, the system bearing all electron-rich groups, **6**, is found to be more stable than cyano-substituted **8**, containing only electron-withdrawing groups, and more stable than the unsubstituted helix, **5**.

When we reexamined the set of meta oligomers used in the validation experiments, we noticed that the relative orientation of side chain functionality (Figure 5) played a significant role in minimizing energies properly. For example, reorientation of the side chain functions influenced ΔH_{helix} by about 0.5 kcal/mol per pair in the case of the methyl ester substituent (the all-syn helix of compound **1** is 3.2 kcal/mol, or 0.5 kcal/mol per pair, less stable than the all-anti), and by a similar value for the methoxyl substituents. The calculations presented in Table 2 have all side chain functions of the helix oriented in the more favorable anti conformation. Therefore, it seemed that side chain functional group orientation influenced the absolute ΔH value obtained from the calculations, indicating that orientation of side chain dipoles is another energy that may contribute to helix stability.[32−37] This additional energy might help explain why the homo ester, **1**, with all electron-poor substituents is predicted to be more stable than **2**, with alternating electron-poor and electron-rich layers, in contrast to classical $\pi-\pi$ stacking arguments. In general, our calculations on *o*-PE oligomers support the hypothesis that orientation of dipoles is an additional factor affecting PE helix stability.[38]

Data for ortho oligomers, in Table 3, contain a number of apparent contradictions that can be clarified by considering the influence of dipoles, including the pair of compounds **6** and **8**, with only OMe and CN substituents, respectively. Because the CN is a rigid side chain, the group dipoles on adjacent layers conflict, reducing the stabilization of the helix to the point that this molecule is our only example that does not minimize to a helical structure. On the other hand, the methoxyl side chain function is conformationally flexible, and can reorient to allow the most favorable dipole orientation. Hence, this helix is more stable than the unsubstituted case, despite the presence of the electron-donating methoxyl groups.

Simple electron-demand arguments based on classical $\pi-\pi$ stacking were insufficient to explain two broad classes of compounds. First, a number of compounds which should have very different overall electron demand (all electron-rich or all electron-poor rings) had similar ΔH_{helix} values. For example, compounds **14b** and **14c** contain aryl ether substituents, yet have ΔH_{helix} values very similar to those of esters **11b** and **11c**. Second, a number of molecules which should have the same helix stabilization energies (identically functionalized *isomers*, including rigid structures) differ in predicted values. When comparing the stacked vs offset isomers (Alt1 and Alt2) within four series of compounds (**9a**−**c**, **11a**−**c**, **12a**−**c**, and **14a**−**c**), calculations predict differences in helix stabilization despite these pairs being identically functionalized isomers with the same electron demand. The offset arrangement of the singly substituted rings apparently provides more flexibility for the dipoles of pendant groups to align favorably, and is more stable than the stacked arrangement in all four cases. This effect persists for molecules with electron-rich substituents (compare ethers **9a**−**c**), electron-withdrawing substituents (compare esters **11a**−**c**), and conformationally locked systems (compare furans **14a**−**c** and lactones **12a**−**c**). Interestingly, in the case of the ester, predictions show that a single substituent will stabilize the helix better than two, which is likely due to unfavorable interactions among these densely packed substituents.

Some of these calculations provide directly testable predictions. However, the relative interlayer orientation of flexible side chains will remain a matter of conjecture until high-resolution structural data becomes available. To provide a more concrete set of predictions, we calculated the helix stabilization energies for a series of cyclic substituents (benzofurans **14a**−**c** and lactones **12a**−**c**) that do not have conformational flexibility, yet offer the chance to set interlayer orientation and hold electron demand constant within the series. Results from these structures bore out the predictions expected if both classical $\pi-\pi$ stacking and dipole orientation energies impact helix stability. Again, a dramatic example comes from the ester series. The molecules in which the lactones are aligned (stacked) (**12a**) or alternated (**12b** and **12c**) differ in helix stabilization energy by a factor of 2, with the aligned molecules being the least stable of the ester-bearing compounds, and the two alternated molecules most stable. Results for the furan and dioxolane series are qualitatively similar, although not as pronounced. It is worthy to note that electron demand of the aromatic ring is apparently reflected in these calculations since

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(38) Calculation of dipole moments of representative monomers shows that the dipole moments roughly parallel the carbonyl bond in esters, and the aliphatic C−O bond in the ethers. Dipole calculations are provided in the Supporting Information.

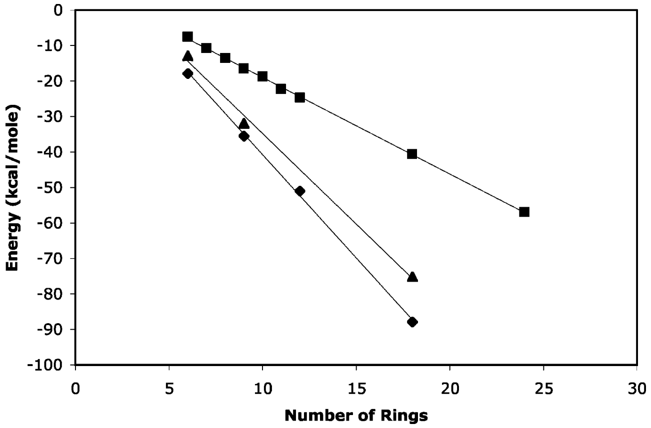

FIGURE 6. MMFF calculated helix formation energy for lactone, furan, and unsubstituted oPE oligomers: lactone (diamonds, slope = 5.8 kcal/mol per repeat unit), furan (triangles, slope = 5.1), and unsubstituted (squares, slope = 2.7).

lactones generally favor helix formation more than ethers, as predicted by $\pi-\pi$ stacking arguments.

The helical forms of isomers can be quite different in predicted energies. For example, lactones **12a**−**c** differ in helix strain energy by 17 kcal/mol, despite being isomeric helices. In addition, the extended form of compound **12b** is 17 kcal/mol less stable than the extended form of **12c**. While the extended forms would not be expected to show any effects of π stacking, the side chains can be close enough to interact. Therefore, the differences in ΔH_{helix} values depend not only on interactions in the helical form but also on the extended structure, particularly when functional groups on adjacent rings are close. This is in sharp contrast to the meta series. That the interaction of polar functional groups occurs both in helical and in extended forms may complicate the analysis of solvent effects on the folding reactions in ortho oligomers.

To assuage our concerns about end effects, three of the series (the unsubstituted form **5**, Alt1 lactone **12b**, and furan **14b**) were extended in length through 24 repeat units. The energies calculated by MMFF were linearly related to oligomer length in all cases (Figure 6). Furthermore, a study of the folding reaction from the extended form, through partially folded intermediates, to the fully folded helix shows a steady decrease in strain energy on increasing ring-to-ring contact, or partial helix formation.[39]

Concluding Remarks

The use of MMFF to calculate structures and ΔH_{helix} for *m*-PEs is surprisingly accurate, and should provide useful insights for the design of *o*-PE foldamer systems. These insights are most likely not sufficiently accurate to replace experiment; however, time and further evaluation will tell if they are accurate enough to provide significant guidance to synthetic efforts. The calculations also point to an additional energy for helix stability—dipole orientation—which should be considered along with $\pi-\pi$ stacking, steric, solvophobic, and entropic considerations when designing helical systems. In addition, some interactions between substituents on adjacent *o*-PE repeat units must be considered, in contrast to the isolation seen in *m*-PEs. In the *o*-PE systems, interlayer relative dipole orientation is an important design criterion and synthetic efforts from our laboratory to test computational predictions on these *o*-PEs will be reported in due course.

Experimental Section

All calculations were performed with the program Spartan '02 (Wavefunction, Inc.). No constraints, either for symmetry or for individual portions of the molecule, were used for any calculation. Starting structures for helix calculations were helical; for extended structures, a completely extended, *transoid* planar structure was used for the meta series, while a completely extended, nearly planar structure was used for the ortho series. For several of the structures, the resulting helical structure was modified slightly to open or close the helix, before running the minimization again, with no significant change in the resulting structure or energy.

A study to evaluate intermediates in the folding reaction was performed and showed a steady decrease in strain energy as more ring-to-ring contacts were made, supporting the comparison of one fully extended structure with its helical counterpart. However, no dynamics calculations have been carried out.[40]

Both MMFF94 and AM1 calculations were performed as implemented in Spartan. The DFT calculations were performed at the BP/DN* level.

Acknowledgment. We gratefully acknowledge helpful discussions with Professor Paul Lahti, Dr. Robert Doerksen, and Dr. Monica Pickholz. Funding was provided by NSF RSEC grant CHE-0223643. G.N.T. thanks the ONR for a Young Investigator Award.

Supporting Information Available: PDB coordinates of all molecules discussed, folding reaction energies and dipole calculations on model monomers. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034827Y

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(39) Supporting Information

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