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COMMUNICATIONS

Published on Web 05/08/2002

The Size-Selective Synthesis of Folded Oligomers by Dynamic Templation

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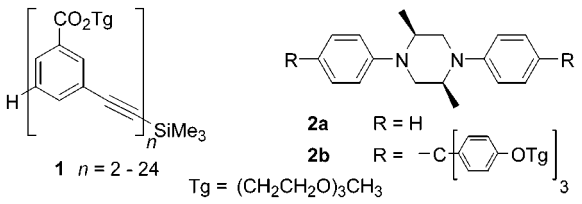
Received January 24, 2002

In recent years, dynamic combinatorial chemistry[1] has attracted attention as a tool for selectively synthesizing molecules according to function, made possible by covalent exchange and supramolecular association to a target.[2−9] Here we extend this to the length-specific synthesis of foldamer-based receptors.[10] In previous studies[11] we have shown that *m*-phenylene ethynylene oligomers **1** fold into macromolecular receptors that bind hydrophobic ligands. These molecules take a helical conformation in polar solvents such as acetonitrile, while exhibiting a random conformation in solvophilic solvents such as chloroform.[11a−b] In the helical conformation they bind nonpolar ligands within the tubular hydrophobic cavity.[11c−e] When the ligand is rodlike molecule **2**, the binding affinity was found to exhibit a maximum for oligomers with $n = 20-22$,[11d−e] and this maximum is accentuated when **2** is capped at its ends with the triphenylmethyl group.[11e] We have also shown that imine metathesis can be used as a reaction for the dynamic synthesis of oligomers, and that the stabilizing energy derived from the helical conformation can shift the equilibrium in favor of oligomers that are folded.[11f] These results impelled us to test the selective synthesis of oligomers using imine metathesis in the presence of the rodlike ligand. Herein we report the size-sselective synthesis of oligomers driven by folding and ligand binding.



The experimental design is illustrated in Figure 1 along with the specific molecules we used. As the starting sequences, we selected 4-mer **3** having two *N*-terminal imines, 6-mer **4a**, and 12-mer **4b**, each having one *C*-terminal imine. Under conditions suitable for imine metathesis, equilibration is established, resulting in a mixture that consists of the three starting substrates, five new oligomers (**5a**, **5b**, **6a**−**c**), and byproduct **7**. We performed the reaction in both dry chloroform and dry acetonitrile at a concentration of 5 mM for each of the starting imines in both the absence and presence (30 mM) of the rodlike molecule **2b**. The reactions were run under nitrogen at room temperature with a catalytic amount (5 mol % of total imine bonds) of oxalic acid. Equilibrium was reached within 2 days as judged by the time-independent product distribution. The final products were analyzed by ^{1}H NMR, MALDI-MS, and silica gel HPLC. The ^{1}H NMR spectra of the reaction mixtures showed that no significant hydrolysis took place during the metathesis reaction, and the MALDI-MS spectra

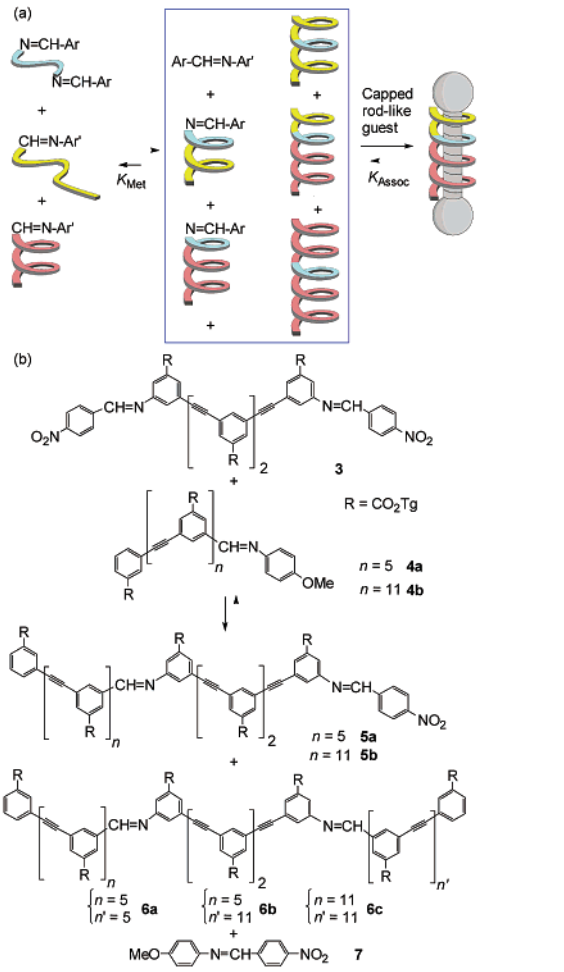


Figure 1. (a) Schematic diagram that illustrates the equilibrium shifting driven by folding and ligand binding. The sequences are color coded. (b) Chemical structure of oligomers used in the metathesis reaction.

exhibited signals for all of the possible products under each of the conditions. The final product distributions of **6a**−**c** were quantitatively determined by the silica gel HPLC analysis.[12]

The equilibrium constant for the imine metathesis reaction is close to unity if there is no extrinsic driving force.[13] Thus, the product distribution of **6a**−**c** in chloroform, where the oligomers have random conformations, is in reasonable agreement with the calculated values based upon the assumption that all of the equilibrium constants for the individual metathesis reactions are unity (Table 1). Moreover, the product distribution in chloroform was not affected by the presence of 2 equiv of ligand **2b**. Metathesis in acetonitrile in the absence of **2b** showed that the formation of **6a**−**c** was significantly increased, as expected.[11f] This equilibrium

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10.1021/ja025698q CCC: $22.00

Table 1. Estimated Yield of **6a**−**c** by HPLC

conditions		estimated yield (%)[a]			
solv	equiv **2b**[b]	**6a**	**6b**	**6c**	total **6**
$CHCl_3$	0	6 ± 1	8 ± 1	5 ± 1	19
calcd[c]	−	8	16	8	−
CH_3CN	0	19 ± 1	37 ± 2	16 ± 1	72
CH_3CN	2	10 ± 1	66 ± 3	9 ± 1	85

[a] Quantitative analysis using peak areas. Error estimates are based on experimental reproducibility of duplicate runs. [b] Equivalents to total amount of starting **3** and **4**. [c] Assumes all metathesis equilibria have equilibrium constants of unity, as expected for $CHCl_3$ data (see text).

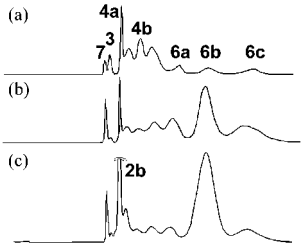

Figure 2. HPLC traces after the metathesis reactions (a) in $CHCl_3$, (b) in CH_3CN and (c) in CH_3CN in the presence of **2b**.

shifting is driven by the stabilizing energy of folding (ΔG_{fold}),[11b,f,14] thus disfavoring those oligomers that are not folded (**3**, **4a**). In fact, ΔG_{fold} for independently synthesized **6a** and **6c** were determined to be 5.5 and 7.5 kcal·mol^{-1}, respectively, as measured by solvent denaturation experiments.[11b,f] This is comparable to ΔG_{fold} of **1** (n = 18, ca. 7.0 kcal·mol^{-1}) despite the presence of two imine bonds that presumably could distort the helical conformation. The observed ratio of **6a**:**6b**:**6c** (ca. 1:2:1) can be rationalized on the basis of a statistical product distribution. Oligomers **6a** and **6c** were formed from **4a**, **5a** and **4b**, **5b**, respectively, while **6b** was formed either from **4a** and **5b**, or from **4b** and **5a**. The free energy change in forming each of the high-molecular weight products **6a**−**c** is expected to be similar.[15]

Most importantly, the product distribution of the metathesis reaction in acetonitrile in the presence of **2b** shifts to favor **6b**, the high-molecular weight oligomer of intermediate length (Figure 2). As shown in Table 1, when 2 equiv of **2b** are present, the total amount of oligomers **6** increases even though the yields of **6a** and **6c** decrease. This is because there is substantial increase in the amount of **6b**. The selective formation of **6b** was predicted since this chain length has the highest affinity for **2b** among the products **6a**−**c**. To estimate the effect of adding the rodlike ligand **2b** to the metathesis reaction, the binding affinities[16] of **6** with **2b** were determined by circular dichroism (CD) measurements.[17] The binding constant for **6** was comparable to that for **1**, and the affinity reached its maximum for the 20-mer **6** ($n = n' = 7$), similar to the case of **1**.[11e] The maximum binding constant of **6** ($n = n' = 7$) to **2b** in acetonitrile was 7.0×10^3 M^{-1}, corresponding to a binding energy of 5.2 kcal·mol^{-1}. On the basis of an equilibrium model and estimations of binding affinity for **6a**−**6c**,[18] we conclude that the enhancement of **6b** in the metathesis reaction in the presence of **2b** was driven by ligand binding—a form of dynamic templation.

In summary, we have shown that the imine metathesis equilibration of helical oligomers can be shifted by ligand binding to enhance the formation of the oligomer with the highest affinity to this ligand. Dynamic templation using a size-selective ligand was demonstrated by selective synthesis of unsymmetrical oligomer **6b**. Since rodlike ligands of different length can be synthesized, the method may be extended to the size-selective synthesis of longer oligomers and polymers.

Acknowledgment. This material is based upon work supported by the National Science Foundation under Grant No. 0106608 and the U.S. Department of Energy, Division of Materials Sciences, under Award No. DEFG02-91ER45439, through the Frederick Seitz Materials Research Laboratory at the University of Illinois at Urbana-Champaign. We thank Dr. Thomas. S. Hughes for discussions on the molecular modeling of the oligomer bound with rodlike ligand.

Supporting Information Available: Synthesis of **3**, **4**, and **6**, ^{1}H NMR, MALDI-MS, and HPLC charts for the products of the metathesis reaction, and nonlinear least-squares fitting curve for binding study, and the molecular modeling of the oligomer bound with rodlike ligand (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) 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. (e) Lehn, J.-M.; Eliseev, A. V. *Science* **2001**, *291*, 2331. (f) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898.

(2) (a) Diederich, F.; Stang, P. J. *Templated Organic Synthesis*; Wiley−VCH: Weinheim, 2000. (b) Summerer, D.; Marx, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 89.

(3) (a) Otto, S.; Furlan, R. L. E.; Sanders J. K. M. *J. Am. Chem. Soc.* **2000**, *122*, 12063. (b) Cousins, G. R. L.; Furlan, R. L. E.; Ng, Y.; Redman, J. E.; Sanders J. K. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 423.

(4) (a) Huc, I.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2106. (b) Polyakov, V. A.; Nelen, M. I.; Nazarpack-Kandlousy, N.; Ryabov, A. D.; Eliseev, A. V. *J. Phys. Org. Chem.* **1999**, *12*, 357. (c) Ramstrom, O.; Lehn, J.-M. *ChemBioChem* **2000**, *1*, 41. (d) Goral, V.; Nelen, M. I.; Eliseev, A. V.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 1347. (e) Moore, J. S.; Zimmerman, N. W. *Org. Lett.* **2000**, *2*, 915.

(5) Karan, C.; Miller, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 7455.

(6) Hiraoka, S.; Fujita, M. *J. Am. Chem. Soc.* **1999**, *121*, 10239.

(7) Crego Calama, M.; Timmerman, P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 755.

(8) Hof, F.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4251.

(9) Nicolau, K. C.; Hughes, R.; Cho, S. Y.; Winssinger, N.; Smethurst, C.; Labischinski, H.; Endermann, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3823.

(10) For a recent review, see Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893.

(11) (a) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793. (b) Prince, R. B.; Saven, J. G.; Wolynes, P. G.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 3114. (c) Prince, R. B.; Barnes, S. A.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 2758. (d) Tanatani, A.; Mio, M. J.; Moore, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 1792. (e) Tanatani, A.; Hughes, T. S.; Moore, J. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 325. (f) Oh, K.; Jeong K.-S.; Moore, J. S. *Nature* **2001**, *414*, 889.

(12) Mixed solvents (NEt_3/*i*-PrOH/$CHCl_3$, 0.02/3.8/96.2) were used as an eluent with a UV detector operating at 290 nm.

(13) Tóth, G.; Pintér, I., Messmer, A. *Tetrahedron Lett.* **1974**, *15*, 735.

(14) Pace, C. N.; Shirley, B. A.; Thomson, J. A. In *Protein Structure: A Practical Approach*; Creighton, T. E., Ed.; IRL Press: New York, 1989; pp 311−330.

(15) Previously, we showed that the folding driving force becomes significant beyond the 6-mer and increases proportionally as the number of repeat units.[11b,f] Thus, the number of repeat units that contribute toward ΔG_{fold}, (i.e., number of repeat unit: 6) is 4 for **5a**, 6 for **4b**, 10 for **5b**, 10 for **6a**, 16 for **6b**, and 22 for **6c**, and the differences between the sum of the folded units on the right and left sides in each equilibrium is 6, respectively, suggesting that the distribution of products **6a**−**c** is not strongly biased by folding.

(16) The program Dynafit was used for nonlinear least-squares fitting; Kuzmic, P. *Anal. Biochem.* **1996**, *237*, 260.

(17) Although **6b** (which is not easily synthesized by conventional methods) was produced as the main product under these metathesis conditions, the purification of the products was not facile, and hence the binding constants for 20-mer **6** ($n = n' = 7$) and 24-mer **6** ($n = n' = 9$) were measured instead. Since the metathesis was conducted in acetonitrile, the binding affinities in acetonitrile were important for the estimation. However, the induced CD signals for **6a** and **6c** in acetonitrile were too small relative to the CD signal caused by excess amount of **2b**. Thus, the measurements were conducted in 40% aqueous acetonitrile (0.1% triethylamine was added to prevent the hydrolysis of imine bonds) from which the binding constant for the series of **6** in acetonitrile could be estimated.

(18) See Supporting Information.

JA025698Q