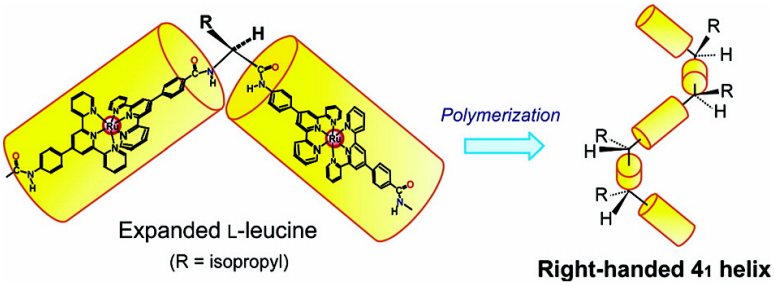
Communication

Right-Handed Helical Structure of Expanded Oligo(l-leucine) Containing [Ru(terpyridine)] Moieties

Taka-aki Okamura, Taku Iwamura, Shuichiro Seno, Hitoshi Yamamoto, and Norikazu Ueyama

J. Am. Chem. Soc., **2004**, 126 (49), 15972-15973• DOI: 10.1021/ja044310j • Publication Date (Web): 19 November 2004



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 11/19/2004

Right-Handed Helical Structure of Expanded Oligo(L-leucine) Containing $[Ru(terpyridine)_2]^{2+}$ Moieties

Taka-aki Okamura, Taku Iwamura, Shuichiro Seno, Hitoshi Yamamoto, and Norikazu Ueyama*

Department of Macromolecular Science, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan

Received September 17, 2004; E-mail: ueyama@chem.sci.osaka-u.ac.jp

The novel design and construction of proteins or macromolecules are believed to provide new, interesting functions, such as molecular recognition, information storage, and catalysis. From this viewpoint, many foldamers have been intentionally synthesized, and their ordered structures have been reported.[1,2] In natural proteins, the conformation is determined predominantly by their amino acid sequences and defined by two torsion angles (ϕ, ψ) for each residue, as shown in the Ramachandran plot.[3,4] The torsion angles are restricted by the polarity and bulkiness of the side chain. The secondary structure is also regulated by intra- or intermolecular hydrophobic and electrostatic interactions, hydrogen bonds,[4] and salt bridges.[5] The type of amino acid residue considerably contributes to the secondary structure; for example, leucine is well-known for exhibiting high helix-forming tendencies.[4,6] In non-natural peptides or foldamers, the helical structure can also be profoundly and rationally altered by the residue.[7]

In this study, a new concept of "expanded L-leucine" is presented, which consists of L-leucine and rigid groups. By using L-leucine, the formation of a chiral secondary structure is expected because poly(L-leucine) forms a right-handed (P) α-helix.[4] As shown in Figure 1a, bis(terpyridine)ruthenium(II) ($Ru(tpy)_2$) was used as a rigid group. $Ru(tpy)_2$ is very popular as a rodlike structure[8−10] and has been utilized as a building block to construct highly sophisticated molecular architectures[11] or metallodendrimers.[12] While $Ru(tpy)_2$-containing polymers have been reported in the literature,[13] using amino acids for directing building blocks is new. Combining such rigid complexes with peptides is known as de novo protein design.[14] The yellow cylinder in Figure 1a, which contains a rodlike complex and amide planes that behave as a rigid group, like a large amide plane, is called an "expanded amide".

Expanded oligo(L-leucine)s, **1**−**4** (Figure 1b), were synthesized by a stepwise N-terminal elongation, including alternate complexation[15,16] and coupling reactions, as shown in Scheme S1 of the Supporting Information. These cationic compounds were purified by chromatography and isolated as PF_6^- salts.

^{1}H NMR and absorption spectra indicated that each $[Ru(tpy)_2]^{2+}$ unit is almost identical. Absorption spectra of **1**−**4** in acetonitrile are shown in Figure 2a, where the vertical axis is the absorption coefficient per $[Ru(tpy)_2]^{2+}$ unit. The spectra are quite similar to each other. The intense absorptions at ca. 300 nm are attributed to $\pi \rightarrow \pi^*$ transitions which are associated with the aromatic rings of the ligand.[17] Metal-to-ligand charge-transfer (MLCT) transitions were observed at 494 nm.[17] The cyclic voltammograms of **1**−**4** in DMF show almost the same figure without a dependence on the length (Figure S6 of the Supporting Information). Reversible Ru(III/II) couples were observed at ca. +1.26 V (vs SCE), and two pseudo-reversible couples attributed to terpyridine moieties were found at −1.17 and −1.39 V. This identity indicates each unit is electrochemically isolated from each other and does not exhibit any significant electronic interactions.

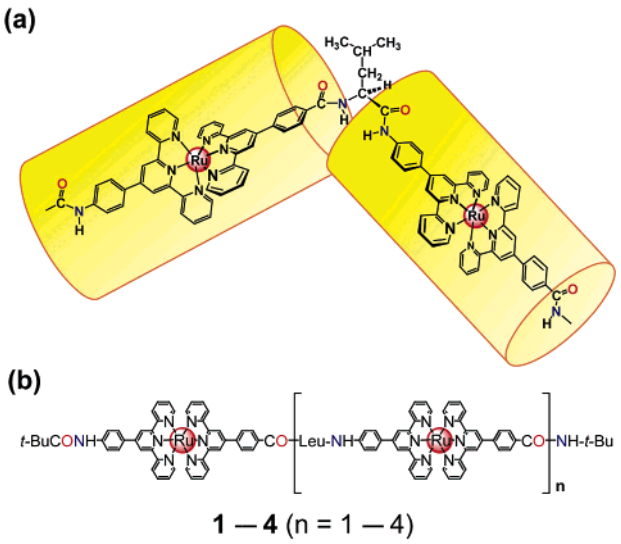


Figure 1. Schematic drawing of (a) expanded L-leucine and (b) expanded oligo(L-leucine).

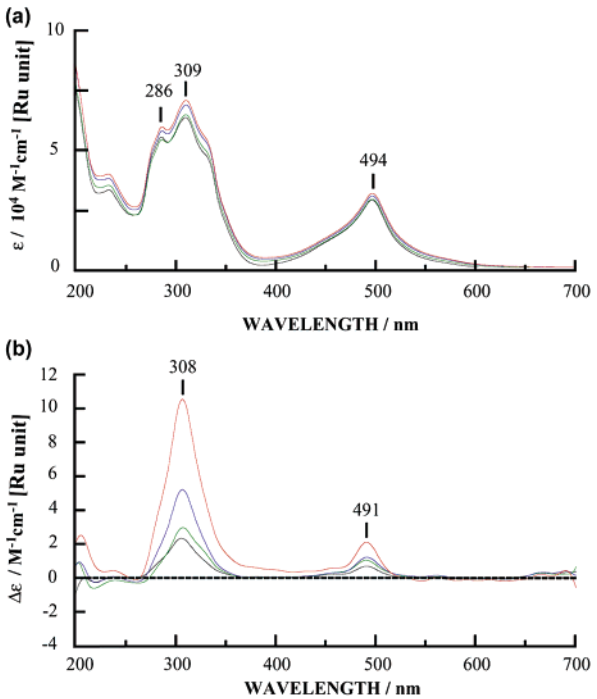


Figure 2. UV−vis (a) and CD (b) spectra of **1** (black), **2** (green), **3** (blue), and **4** (red) in acetonitrile at 30 °C. The vertical axis is normalized for the concentration of the ruthenium unit.

In contrast with these results, CD spectra in the same region exhibit striking enhancement of the intensity per ruthenium ion with

10.1021/ja044310j CCC: $27.50

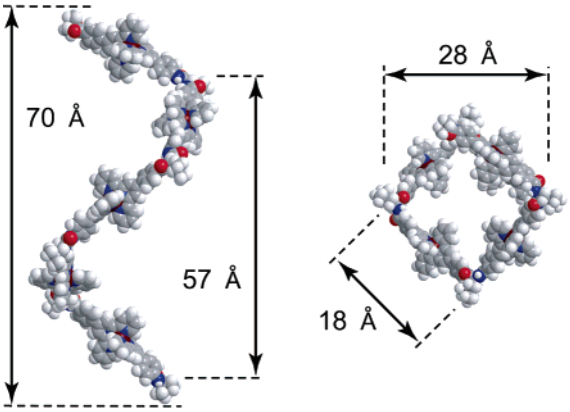


Figure 3. Solution structure of tetramer **4** based on the ^{1}H NMR analysis; side (left) and top (right) views.

elongating peptide chain (Figure 2b). The CD spectra do not show typical exciton splitting, which is attributed to electric dipole moments in chromophores and is usually observed in chiral octahedral complexes.[17,18] Thus, the intense positive Cotton effects predominantly arise from electron movement along a right-handed (P) helix, as found in helicates.[18−20] The enhancement of the CD signal indicates the formation of a well-defined helical structure.

The solution structure was determined by ^{1}H NMR measurements and molecular dynamics. ^{1}H NMR spectra of **4** in acetonitrile-d_3 show that the four residues are identical. Conformation of the leucine residue was determined by the simulated annealing (SA) method[21,22] using the NMR constraints of **4**. The obtained lowest-energy structure and the reported crystal structure[23] of $[Ru(tpy)_2]^{2+}$ were applied to the molecular dynamics calculation[24] of **4.** The final structure is shown in Figure 3. The molecule exhibits a right-handed (P) 4_1 helix with two dihedral angles ($\phi = -146°$, $\psi = 30°$), which are appropriate for $n = 4$ (n is the number of residues per turn).[25,26] The pitch is calculated to be 57 Å, and the dimensions of the helix are $18 \times 28 \times 70$ Å^3.

In summary, we have defined and constructed "expanded oligo(L-leucine)". The helical structure is determined by two torsion angles, ϕ and ψ. Electrostatic repulsion between dicationic ruthenium moieties probably contributes to the stabilization of the extended helix with a long pitch. When a more polar solvent, such as dimethyl sulfoxide (DMSO), was used instead of acetonitrile, the intensity of CD decreased (Figure S7 of the Supporting Information). However, the most important factor is restriction of the torsion angles (ϕ, ψ). Even if a neutral rigid group is used (e.g., *t*-BuCONHC$_6$H$_4$CO−(Leu-NHC$_6$H$_4$CO)$_n$-NH-*t*-Bu), the normalized CD intensity increased with the elongation of peptide chain (Figure S8 of the Supporting Information). These results suggest that the electrostatic repulsion is not essential but affects the stabilization; additionally, the thermal motion breaking the whole helical structure is limited in the longer chain.

The modification of the peptide is performed easily by the replacement of $[Ru(tpy)_2]^{2+}$ with various rigid groups. This result could trigger a wide variety of other parallel studies, such as various expanded poly(L-leucine)s or expanded poly(α-amino acid)s, which will lead to new functionalized molecules.

Acknowledgment. This work was supported by the Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Experimental details for the synthesis, physical measurements of all compounds, and structural determination of **4**, including ^{1}H NMR, NOESY, CV, and the related spectra (Scheme S1 and Figures S1−S8). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180.
(2) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4011.
(3) Ramakrishnan, C.; Ramachandran, G. N. *Biophys. J.* **1965**, *5*, 909−933.
(4) Schulz, G. E.; Schirmer, R. H. *Principles of Protein Structure*; Springer-Verlag: New York, 1979.
(5) Padmanabhan, S.; Baldwin, R. L. *J. Mol. Biol.* **1994**, *241*, 706−713.
(6) Finkelstein, A. V.; Ptitsyn, O. B. *J. Mol. Biol.* **1976**, *103*, 15−24.
(7) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J., Jr.; Gellman, S. H. *Nature* **1997**, *387*, 381−384.
(8) Barigelletti, F.; Flamigni, L.; Balzani, V.; Collin, J.-P.; Sauvage, J.-P.; Sour, A.; Constable, E. C.; Thompson, A. M. W. C. *J. Am. Chem. Soc.* **1994**, *116*, 7692−7699.
(9) Kelch, S.; Rehahn, M. *Chem. Commun.* **1999**, 1123−1124.
(10) Janini, T. E.; Fattore, J. L.; Mohler, D. L. *J. Organomet. Chem.* **1999**, *578*, 260−263.
(11) Schubert, U. S.; Eschbaumer, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2893−2926.
(12) Newkome, G. R.; He, E.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689−1746.
(13) Lohmeijer, B. G. G.; Schubert, U. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3825−3829. (b) Lohmeijer, B. G. G.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 1413−1427.
(14) Schneider, J. P.; Kelly, J. W. *Chem. Rev.* **1995**, *95*, 2169−2187.
(15) Storrier, G. D.; Colbran, S. B. *Inorg. Chim. Acta* **1999**, *284*, 76−84.
(16) Storrier, G. D.; Colbran, S. B.; Craig, D. C. *J. Chem. Soc., Dalton Trans.* **1997**, 3011−3028.
(17) Ziegler, M.; Monney, V.; Stoeckli-Evans, H.; Von Zelewsky, A.; Sasaki, I.; Dupic, G.; Daran, J.-C.; Balavoine, G. A. *J. Chem. Soc., Dalton Trans.* **1999**, 667−675.
(18) Ziegler, M.; Von Zelewsky, A. *Coord. Chem. Rev.* **1998**, *177*, 257−300.
(19) Baum, G.; Constable, E. C.; Fenske, D.; Housecroft, C. E.; Kulke, T. *Chem. Commun.* **1998**, 2659−2660.
(20) Piguet, C.; Bernardinelli, G.; Hopfgarner, G. *Chem. Rev.* **1997**, *97*, 2005−2062.
(21) Brünger, A. T. *X-PLOR, Version 3.1: A System for X-ray Crystallography and NMR;* Yale University Press: New Haven, CT, 1993. The latest version (3.851) was obtained over the Internet (URL http://xplor.csb.yale.edu) and used.
(22) Nilges, M.; Gronenborn, A. M.; Brünger, A. T.; Clore, G. M. *Protein Eng.* **1988**, *2*, 27−38.
(23) Craig, D. C.; Scudder, M. L.; McHale, W.-A.; Goodwin, H. A. *Aust. J. Chem.* **1998**, *51*, 1131−1139.
(24) *Insight II 2000*; Accelrys Inc.: San Diego, CA, 2000.
(25) Dickerson, R. E.; Geis, I. *The Structure and Action of Proteins*; Harper & Row: New York, 1969.
(26) Edsall, J. T.; Flory, F. J.; Kendrew, J. C.; Liquori, A. M.; Némethy, G.; Ramachandran, G. N. *J. Mol. Biol.* **1966**, *15*, 399−407.

JA044310J