ORGANIC LETTERS

2008
Vol. 10, No. 21
5035−5038

Folding-Induced Selective Hydrogenation of Helical 9,10-Anthraquinone Analogues

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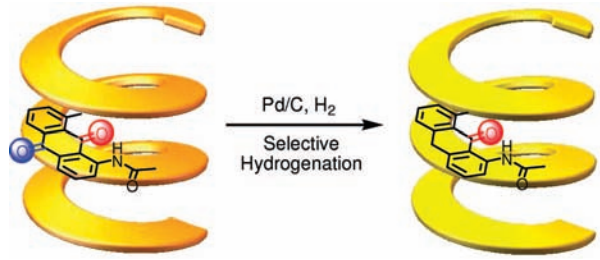
Received September 26, 2008

ABSTRACT



The first selective catalytic hydrogenation induced by the artificial helix based on oligo(phenanthroline dicarboxamide)s containing a 9,10-anthraquinone subunit is described. Due to the steric hindrance within the helically folded oligomers, the selective reductions of the anthraquinone units were completely different from those of model substrates, which subsequently mimicked the enzyme catalysis for preventing some reactions from occurring.

In the past decade, synthetic helical foldamers[1] have attracted great attention for mimicking the structures and functions of biological macromolecules and showing potential applications in material sciences and supramolecular chemistry. Consequently, numerous helical foldamers have been designed and synthesized by different strategies.[1,2] The specific chemical environments provided by foldamers not only mimic the catalytic behavior of biological systems for reactions[3] but also prevent some reactions from occurring.[4] However, studies of foldamer reactivity are still fewer in number. One particular study carried out by Moore's group involved the methylation of a dimethylaminopyridine unit placed in the backbone of mPE foldamers using a methylating agent, which acted as a "reactive sieve" for different sizes and different shapes of guest substrates.[5] Another special example reported by Huc's group[6] is about the pyridine N-oxidation of the helical oligopyridine dicarboxa-

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(1) (a) Hecht, S. M.; Huc, I. *Foldamers: Structure, Properties and Applications*; Wiley-VCH: Weinheim, Germany, 2007. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180. (c) Hill, D. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011.

(2) Some recent reviews see: (a) Huc, I. *Eur. J. Org. Chem.* **2004**, *1*, 17–29. (b) Gong, B.; Sanford, A. R.; Ferguson, J. S. *Adv. Polym. Sci.* **2007**, *206*, 1–29. (c) Li, Z.-T.; Hou, J.-L.; Li, C.; Yi, H.-P. *Chem. Asian J.* **2006**, *1*, 766–778. (d) Davis, J. M.; Tsou, L. K.; Hamilton, A. D. *Chem. Soc. Rev.* **2007**, *36*, 326–334.

(3) (a) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170–177. (b) Smaldone, R. A.; Moore, J. S. *Chem.−Eur. J.* **2008**, *14*, 2650–2657.

(4) (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647–1668. (b) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997–2011. (c) Vriezema, D. M.; Aragonès, M. C.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445–1489. (d) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146–153.

(5) (a) Heemstra, J. M.; Moore, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 1648–1649. (b) Heemstra, J. M.; Moore, J. S. *J. Org. Chem.* **2004**, *69*, 9234–9237. (c) Smaldone, R. A.; Moore, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 5444–5450. (d) Smaldone, R. A.; Moore, J. S. *Chem. Commun.* **2008**, 1011–1013.

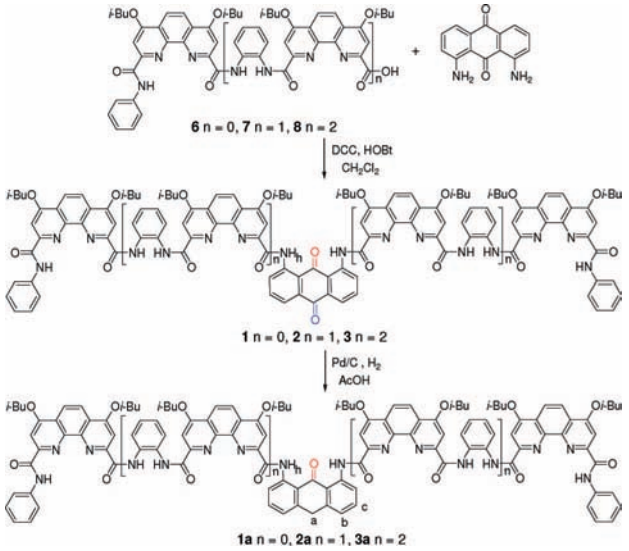
(6) Dolain, C.; Zhan, C.; Léger, J. M.; Daniels, L.; Huc, I. *J. Am. Chem. Soc.* **2005**, *127*, 2400–2401.

10.1021/ol802241h CCC: $40.75
Published on Web 10/10/2008

mide strands. The same group recently also reported an interesting selective bromination of helically folded oligoamides by *N*-bromosuccinimide.[7]

Recently, we reported a new class of phenanthroline-derived oligoamide helical foldamers.[8] Due to their small helical hollows and extremely compact structures, we envisioned that the active group inside the helical cavity could be well-protected against some reactions from occurring. Consequently, we designed and synthesized the oligomers **1**∼**3** (Scheme 1), in which the reactive 9,10-anthraquinone unit was positioned at the midpoint of the helical foldamer's backbone. Herein, we report the folding-induced selective hydrogenation of the helical anthraquinone analogues to give the new helical foldamers **1a**∼**3a**. To our knowledge, this is the first selective reduction of the single artificial helix, which shows completely different catalytic hydrogenation from the mode reaction of diacetamide anthraquinone.

Scheme 1. Synthesis and Selective Catalytic Hydrogenations of Oligomers **1**∼**3**



The oligomers **1**∼**3** were synthesized by the reaction of the appropriate monoacid[8a] with 1,8-diaminoanthracene-9,10-dione in dichloromethane in the presence of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole (Scheme 1). Similar to the oligo(phenanthroline dicarboxamide)s previously reported,[8] the ^{1}H NMR and 2D NOESY studies clearly supported formation of the helical secondary structures of oligoamides **1**∼**3** in solution.[9] The UV/vis absorption spectra further confirmed the intramolecular interactions of the helical foldamers (Figure 1, solid line). As expected, a hypochromic effect with an increasing number of phenanthroline rings was observed, indicating the formation of the helical ordering and $\pi-\pi^*$ stacking of the phenanthroline units (λ_{max} = ∼330 nm) in **1**∼**3**.[9,10]

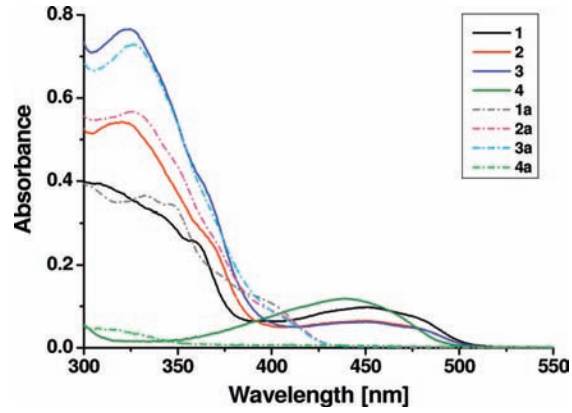


Figure 1. UV−vis spectra of the molecular strands **1**∼**4** (solid line) and **1a**∼**4a** (dash line) in $CHCl_3$ ($c = 1.0 \times 10^{-5}$ M).

A single crystal of oligomer **2** suitable for X-ray diffraction was obtained by slow evaporation of a solution of CH_2Cl_2/EtOH.[11] The crystal structure showed that oligomer **2** adopts a regular helical secondary structure, and the two carbonyl groups of the 9,10-anthraquinone unit position inside and outside the helical hollow, respectively (Figure 2), which implies the two carbonyls can show different catalytic hydrogenation activities.[12]

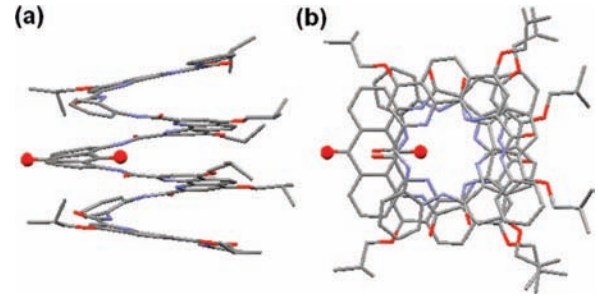


Figure 2. Side view (a) and top view (b) of the crystal structure of **2**. Solvent molecules and hydrogen atoms have been omitted for clarity.

The catalytic hydrogenations were performed under a hydrogen atmosphere in acetic acid in the presence of 10% Pd/C. We first tested the hydrogenation of diacetamide

(7) Srinivas, K.; Kauffmann, B.; Dolain, C.; Léger, J. M.; Ghosez, L.; Huc, I. *J. Am. Chem. Soc.* **2008**, *130*, 13210–13211.

(8) (a) Hu, Z.-Q.; Hu, H.-Y.; Chen, C.-F. *J. Org. Chem.* **2006**, *71*, 1131–1138. (b) Hu, H.-Y.; Xiang, J.-F.; Yang, Y.; Chen, C.-F. *Org. Lett.* **2008**, *10*, 69–72. (c) Hu, H.-Y.; Xiang, J.-F.; Yang, Y.; Chen, C.-F. *Org. Lett.* **2008**, *10*, 1275–1278.

(9) See Supporting Information.

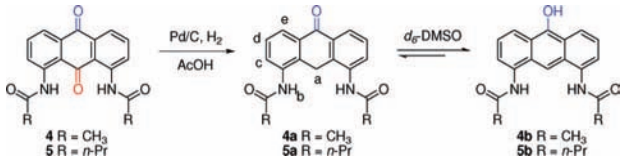
(10) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793–1796.

(11) Crystal data for **2**·6(C_2H_5OH)·2(H_2O): $C_{138}H_{160}N_{16}O_{26}$; M_w = 2458.82; triclinic; space group *P*-1; a = 16.062(4) Å, b = 20.088(5) Å, c = 22.642(6) Å; α = 84.27(3)°, β = 70.17(2)°, γ = 67.43(3)°; V = 6342(3) Å^3; Z = 2; T = 112(2) K; R_1 =0.2082; wR_2 = 0.4190 (all data); R_1 = 0.1533, wR_2 = 0.3804 [$I > 2\sigma(I)$].

(12) Maurizot, V.; Dolain, C.; Leydet, Y.; Léger, J. M.; Guionneau, P.; Huc, I. *J. Am. Chem. Soc.* **2004**, *126*, 10049–10052.

anthraquinone (**4**) as the model[13] and found the reaction could be finished in 45 min to give the anthrone **4a** in a quantitative yield (Scheme 2). It was found that compound

Scheme 2. Selective Catalytic Hydrogenation of Diacetamide Anthraquinones **4** and **5**



4a did not dissolve in $CDCl_3$, and the ^1H NMR spectrum in d_6-DMSO showed that **4a** could be transformed into anthrol **4b**. After 1 day, almost no changes of the spectrum occurred,[9] in which the tautomeric constant ([anthrone]/[anthrol]) was found to be approximately 1/1.8.[14] We also synthesized dibutyramide anthraquinone **5** but found that its hydrogenation product **5a** did not dissolve in $CDCl_3$ either.[9,15]

The first evidence for the hydrogenation of **4** came from the UV/vis absorption spectrum, in which the characteristic absorption of the anthraquinone chromophore at ~440 nm disappeared (Figure 1, green dash line). The ^1H and ^{13}C NMR and MS spectra were also in agreement with the structure of anthrone **4a**, which was further established by the TOCSY and NOESY spectra. In the TOCSY spectrum of **4a**, no cross peaks between H_a and the aryl protons H_c-H_e were observed.[9] Meanwhile, the NOESY spectrum of **4a** also exhibited no cross peaks between H_a and the aryl protons H_c-H_e but the expected correlation between proton H_a and the NH proton H_b (Figure 3). These observations indicated

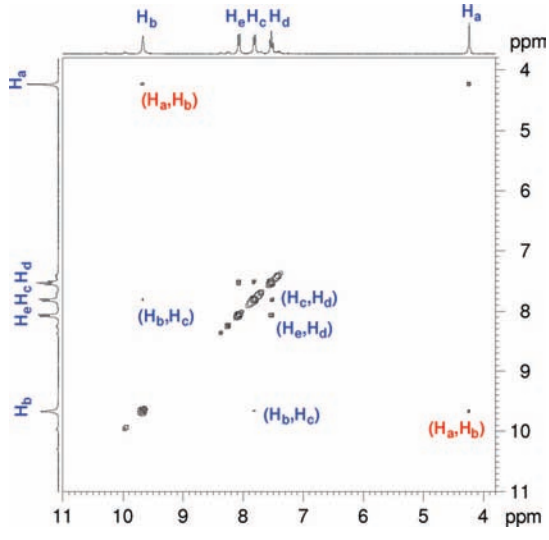


Figure 3. Partial NOESY spectrum (600 MHz, d_6-DMSO) of **4a**.

that the hydrogenation of **4** selectively occurred on the inside carbonyl group to give product **4a**. Moreover, we have also attempted to obtain the crystals of the anthrones. Although we have not succeeded so far, the crystals of a dianthrone derivative of **4a** suitable for X-ray analysis were unexpectedly obtained by slow diffusion of ether into a solution of **4a** in DMF,[16,17] and its crystal structure provided an accessorial evidence for the structure of **4a** (Figure 4).

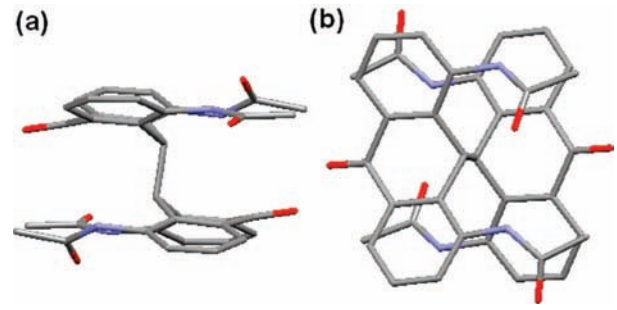


Figure 4. Side view (a) and top view (b) of the crystal structure of the dianthrone. Hydrogen atoms have been omitted for clarity.

Under the same conditions as above, it was interestingly found that the catalytic hydrogenations of oligomers **1**~**3** selectively occurred on the outer carbonyl group to give the anthrone analogues **1a**~**3a** in high yields. It was different from the model compound **4** that oligomers **1a**~**3a** did not dissolve in d_6-DMSO, but they were found to be stable in $CDCl_3$ for more than one month. Compared with oligomers **1**~**3**, the characteristic absorption band of the anthraquinone chromophore at ~440 nm disappeared in the UV−vis absorption spectra of **1a**~**3a** (Figure 1, dash line), while the absorption bands of the phenanthroline rings were still identical to those of **1**~**3**, which implied that oligomers **1a**~**3a** were also in helical structures. Moreover, the ^1H NMR spectra of **1a**~**3a** showed a new peak for the methylene proton H_a but no obvious changes for the shifts of N*H* zone signals, especially the proton H_h signal (Figure 5). The results not only suggested the formation of the anthrones but also indicated the maintained helical conformation of the oligomers.

Structures of the oligomers **1a**~**3a** were further proved by their TOCSY and NOESY spectra.[9] In the NOESY spectra of **2a**, a cross peak between proton H_a and proton

(13) To our surprise, no reductions of diacetamide anthraquinones were hitherto reported.

(14) McCann, G. M.; McDonnell, C. M.; Magris, L.; O'Ferrall, R. A. M. *J. Chem. Soc., Perkin Trans. 2* **2002**, 784–795.

(15) We also synthesized di(*n*-decanamide) anthraquinone (R = *n*-C_9H_{19}) but found that its hydrogenation product did not dissolve in either $CDCl_3$ or d_6-DMSO.

(16) The reaction mechanism for formation of the dianthrone is not clear, which might be through a photoreaction under the influence of sunlight and air. For a similar reaction, see: Schönebrg, A.; Mustafa, A. *J. Chem. Soc.* **1945**, 657–660. In addition, owing to the poor solubility of the dianthrone in common solvents, it has not been characterized by NMR and MS spectra.

(17) Crystal data for the dianthrone: $C_{36}H_{30}N_4O_6$; M_w = 614.64; monoclinic; space group $P2(1)/n$; a = 8.0388(16) Å, b = 11.363(2) Å, c = 16.369(3) Å; α = 90.00°, β = 94.27(3)°, γ = 90°; V = 1491.1(5) Å^3; Z = 2; T = 173(2) K; R_1 = 0.0907; wR_2 = 0.1561 (all data); R_1= 0.0644, wR_2 = 0.1455 [$I > 2\sigma(I)$].

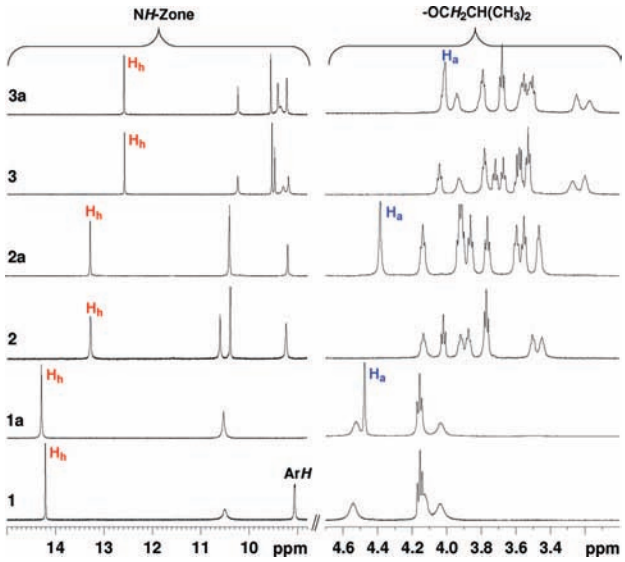


Figure 5. Partial ^{1}H NMR spectra (600 MHz, $CDCl_3$) of oligomers **1**∼**3** and **1a**∼**3a** (5.0 mM).

H_b was shown, while no cross peaks between H_a and the NH protons H_h were observed, which were all in agreement with the structure of **2a**. Moreover, the TOCSY spectrum of **2a** also showed the expected correlations between proton H_a and protons H_b and H_c (Figure 6), which further provided unambiguous evidence for the selective hydrogenation of **2** occurring on the outer carbonyl group to give product **2a**. This result is completely different from that of the model reaction, in which the presence of diacetamide units might make the adjacent keto groups bind with the catalyst more stably and subsequently yield the selective reduction products of anthrones. For oligomers **1**∼**3**, the selective catalytic hydrogenation is most likely caused by the steric hindrance within the helically folded oligomers.

In conclusion, we have presented the first selective reduction induced by a single artificial helix based on oligo(phenanthroline dicarboxamide)s containing a 9,10-anthraquinone subunit. Due to the steric hindrance within the helically folded oligomers, the selective catalytic hydrogenation of the anthraquinone unit was completely different from that of model substrates. The results presented here cannot only mimic the enzyme catalysis for preventing some reactions from occurring but also provide a convenient method to synthetic new helical foldamers. Further studies will attempt to build higher-ordered structures by the coupling reactions[16] of the helical anthrone analogues and will also focus on the design of reactions in which the oligomers have potential to act catalytically.

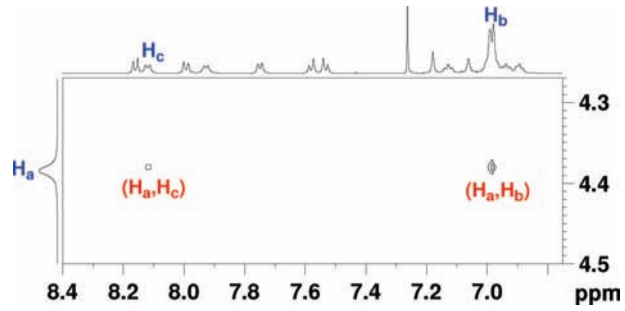


Figure 6. Partial TOCSY spectrum (600 MHz, $CDCl_3$) of oligomer **2a**.

Acknowledgment. We thank the National Natural Science Foundation of China (20625206) and the National Basic Research Program (2007CB808004, 2008CB617501) for financial support. We also thank Dr. Hai-Bin Song at Nankai University for determining the crystal structures.

Supporting Information Available: Synthesis and characterization data of new compounds. Copies of ^{1}H and ^{13}C NMR spectra. TOCSY, NOESY, and UV−vis spectra of **1**∼**4** and **1a**∼**4a**. The X-ray crystallographic files (CIF) for **2** and the dianthrone derivative of **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802241H